DISSERTATION ON

A STUDY ON "ASSOCIATION BETWEEN METABOLIC SYNDROME AND ACUTE CORONARY SYNDROME"

DISSERTATION SUBMITTED TO

THE TAMILNADU DR. M.G.R MEDICAL UNIVERSITY,

IN PARTIAL FULFILLMENT OF THE

RULES AND REGULATIONS FOR THE AWARD OF THE

M.D. DEGREE IN GENERAL MEDICINE

BRANCH – I

THANJAVUR MEDICAL COLLEGE

THANJAVUR – 613004

MAY – 2018

Thanjavur Medical College

THANJAVUR, TAMILNADU, INDIA - 613001

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INSTITUTIONAL ETHICAL COMMITTEE

CERTIFICATE

Approval No. : 385

This is to certify that The Research Proposal / Project titled

ASSOCIATION BETWEEN METABOLIC SYNDROME AND ACUTE CORONARY SYNDROME

submitted by Dr. SANGEETHA . G **of**

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was approved by the Ethical Committee.

Thanjavur

Dated : 01.03.2017

THANJAVUR MEDICAL COLLEGE ETHICAL COMMITTEE THANJAVUR

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INSTITUTIONAL ETHICAL COMMITTEE
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THANJAVUR

CERTIFICATE

This is to certify that dissertation entitled "**A STUDY ON "ASSOCIATION BETWEEN METABOLIC SYNDROME AND ACUTE CORONARY SYNDROME"** is the bonafide record of work done by **DR.G.SANGEETHA** in the Department of General Medicine, Thanjavur Medical College, Thanjavur during his Post Graduate Course from 2015 – 2018. This is submitted as partial fulfillment for the requirement of M.D. Degree Examinations – Branch I (General Medicine) to be held in May 2018

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DECLARATION

I, **DR. G.SANGEETHA**, solemnly declare that dissertation titled "**A STUDY ON ASSOCIATION BETWEEN METABOLIC SYNDROME AND ACUTE CORONARY SYNDROME"** is a bonafide work done by me at Thanjavur medical college & Hospital during March 2017 –August 2017 under the guidance of Professor - **Dr. Dr.K.Namasivayam, M.D.,**

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ACKNOWLEDGEMENT

I wish to express my sincere thanks to our respected **Dean Dr.S. JEYA KUMAR MS.,Mch, FRCS**., for having allowed me to conduct this study in our hospital.

I express my heartfelt thanks and deep gratitude to the Head of the Department of Medicine and chief, Prof.**Dr.D. NEHRU, M.D, DMRD.,**. for his generous help and guidance in the course of the study.

I sincerely thank my Guide , Professor - **Dr. Dr.K.Namasivayam, M.D.,** and my Asst. Professors - **Dr.R.T.SHRIRAM GANESH . MD, D.A, DR.N. RAMESH M.D,** for their guidance and kind help.

My sincere thanks to all my friends and post-graduate colleagues for their whole hearted support and companionship during my studies.

I thank all my **PATIENTS**, who formed the backbone of this study without whom this study would not have been possible.

Lastly, I am ever grateful to the **ALMIGHTY GOD** for always showering His blessings on me and my family.

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CERTIFICATE – II

This is to certify that this dissertation work titled "**A STUDY ON ASSOCIATION BETWEEN METABOLIC SYNDROME AND ACUTE CORONARY SYNDROME** " of the candidate DR.G. SANGEETHA with registration Number 201511207 for the award of M.D in the branch of General Medicine. I personally verified the urkund.com website for the purpose of plagiarism Check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows *1% (one percentage*) of plagiarism in the dissertation.

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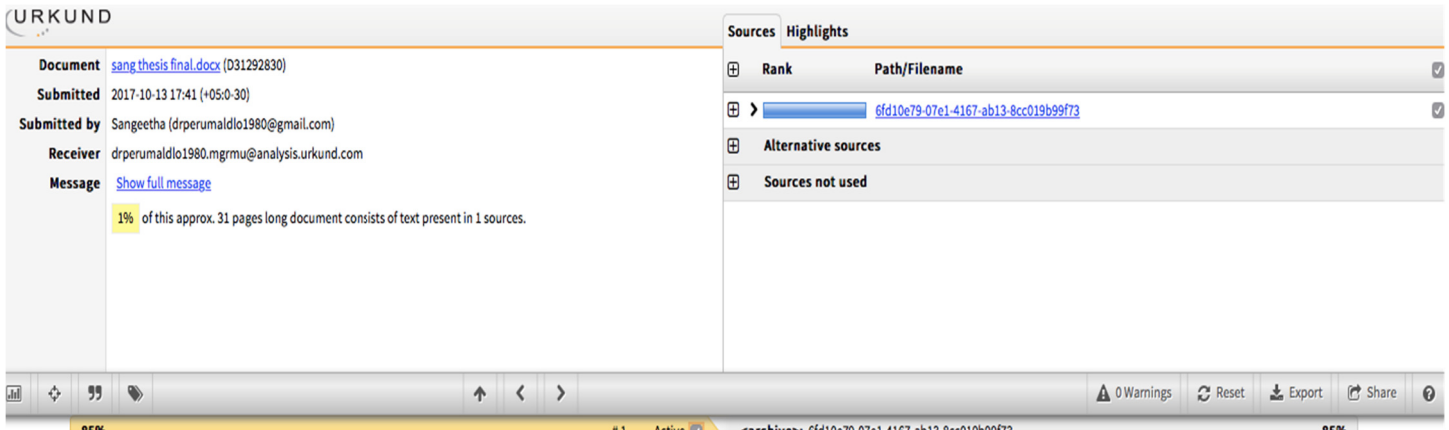

provisional report of a WHO consultation. DiabetMed 1998;15:539-53.

4. Ineternational Diabetes Federation .Worldwide definition of the metabolic syndrome. Available atwww.idf.org/webdata/docs/IDF_Metabolic syndrome _definition.pdf.

5.Metabolic syndrome – Harrison's principles of medicine 17th edition vol ii.

6.Zeller M, Steg PG, Ravisy J, Laurent Y, Janin-Manificat L, L'Huillier I, et al . Prevalence and impact of metabolic syndrome on hospital outcomes in acute myocardial infarction. Arch IntenMed 2005;165:1192-8.

7. Reaven GM. Banting Lecture 1988: role of insulin resistance in human disease. Diabetes.1988;37:1595-1607.

8. Savage et al., Human Metabolic syndrome resulting from dominant – negative mutations in nuclear receptor – gamma. Diabetes, 52,910-917.

9. Song, Y., Niu, T., Manson, J.E., Kwiatkouski, D., Liu, S.2004.Are variants in CAPN 10 gene related to risk of type 2 diabetes? A quantitative assessment of population & family – based association studies. Am.J.Hum.Genet, 74, 208-222.

10. Weedon, M.N., Gloyn, A.L., Frayling, T.M., Hattersley, A.T.,Datey Smith, G., Ben-shloma, Y.2003a. Quantitative traits associated with the Type 2 diabetes susceptibility allele on Kir 6.2.

11. International journal of paediatric research 2006 12. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. JAMA.2002; 287: 356-359.

13. Reaven G. The metabolic syndrome or the insulin resistance syndrome? Different names, different concepts, and different goals. EndocrinolMetabClin North Am. 2004; 33: 283-303

ABBREVIATIONS

MS-METABOLIC SYNDROME

STEMI-ST ELEVATION MI

NSTEMI-NON ST ELEVATION MI

FBS-FASTING BLOOD SUGAR

BP-BLOOD PRESSURE

TG-TRIGLYCERIDES

WC-WAIST CIRCUMFERENCE

HDL-HIGH DENSITY LIPOPROTEIN

VLDL-VERY LOW DENSITY LIPOPROTEIN

TNF-TUMOUR NECROSIS FACTOR

PAI-PLASMINOGEN ACTIVATOR INHIBITOR

ADA - AMERICAN DIABETES ASSOCIATION

BMI – BODY MASS INDEX

CAD – CORONARY ARTERY DISEASE

CAHD - CORONARY ARTERY HEART DISEASE

ICCU - INTENSIVE CORONARY CARE UNIT

IHD - ISCHEMIC HEART DISEASE

LDL – LOW DENSITY LIPOPROTEIN

NCEP -NATIONAL CHOLESTEROL EDUCATION PROGRAM

NON-MS -NON METABOLIC SYNDROME

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INTRODUCTION

The metabolic syndrome (syndrome X, insulin resistance syndrome) consists of a group of metabolic abnormalities that confer increased risk of cardiovascular disease (CVD) and diabetes mellitus. Evolution of the criteria for the metabolic syndrome since the original definition by the World Health Organization (WHO) in 1998 reflects growing clinical evidence and analysis by a variety of consensus conferences and professional organizations that led to the increasing understanding of this syndrome. The major features of the metabolic syndrome include central obesity, hyper triglyceridemia, low levels of high-density lipoprotein (HDL) cholesterol, hyperglycemia, and hypertension.

RISK FACTORS

Overweight/Obesity

Although the metabolic syndrome was first described in the early twentieth century, the worldwide overweight/obesity epidemic has recently been the force that driving its increasing recognition and treatment. Central adiposity is a key feature of the syndrome, and the syndrome's prevalence reflects the strong relationship between waist circumference and increasing adiposity and increasing weight. However, despite the importance of obesity, patients who are of normal weight may also be insulin resistant and may have the metabolic syndrome and associated morbidity.

Sedentary Lifestyle

Physical inactivity is a predictor of CVD events and the related increased risk of death. Many components of the metabolic syndrome are associated with a sedentary lifestyle, including increased adipose tissue (predominantly central) accumulation, reduced HDL cholesterol level, and increased triglycerides, blood pressure, and glucose in genetically susceptible population. Compared with individuals who watch television or videos or use the computer <1 h daily, those who do so for >4 h daily have a twofold increased risk of the metabolic syndrome and related risk of death.

Aging

The metabolic syndrome affects nearly 50% of the U.S. population older than age 50 years and at >60 years of age women are more often affected than men. The age dependency of the syndrome's prevalence is seen in most populations around the world in most of the countries.

Diabetes Mellitus

Diabetes mellitus is included in both the national cholesterol educational program and the harmonizing definitions of the metabolic syndrome. It is estimated that the great majority (~75%) of the patients with type 2 diabetes or the impaired glucose tolerance have the metabolic syndrome. The presence of the metabolic syndrome in these populations around the world relates to a

higher prevalence of cardiovascular disease than in patients who have type 2 diabetes or impaired glucose tolerance but do not have the metabolic syndrome.

Cardiovascular Disease

Individuals with the metabolic syndrome are twice as likely to die of cardiovascular disease as those who do not have the syndrome,and their risk of an acute myocardial infarction or stroke is threefold higher than those who do not have the syndrome. The approximate prevalence of the metabolic syndrome among patients with coronary heart disease (CHD) is 50%, with a prevalence of ~35% among patients with premature coronary artery disease (before or at age 45) and a particularly high prevalence among women than men. With appropriate cardiac rehabilitation and changes in lifestyle (e.g., nutrition, physical activity, weight reduction, and—in some cases—pharmacologic therapy, appropriate diet), the prevalence of the syndrome can be reduced to a satisfactory level.

Lipodystrophy

Lipodystrophic disorders in general are associated with the metabolic syndrome. Both genetic form of lipodystrophy (e.g., Berardinelli- Seip congenital lipodystrophy, Dunnigan familial partial lipodystrophy) and acquired form of lipodystrophy (e.g., HIV-related lipodystrophy in higher prevalence of cardiovascular disease than in patients who have type 2 diabetes mellitus or impaired glucose tolerance but do not have this syndrome.

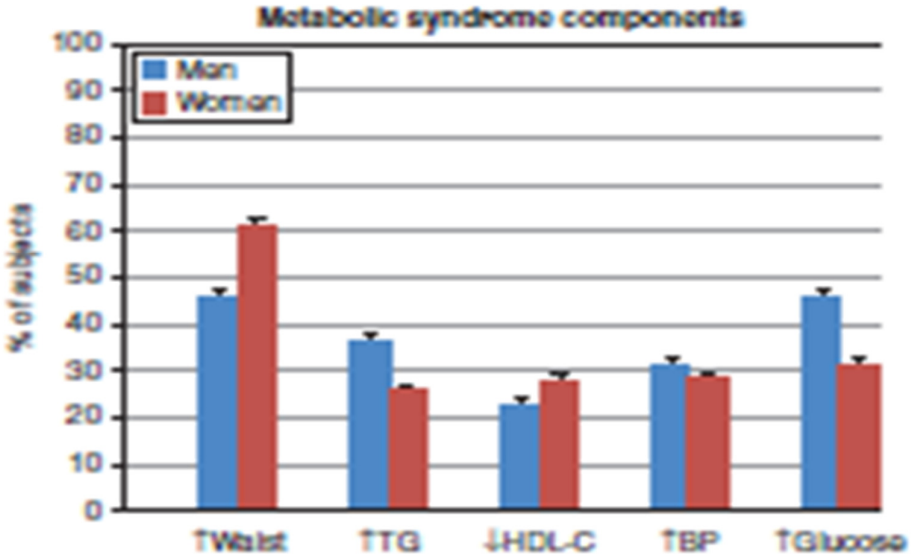


FIGURE 422-1 Prevalence of the metabolic syndrome components, from NHANES 2003–2006. NHANES, National Health and Nutrition Examination Survey; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; BP, blood pressure. The prevalence of elevated glucose includes individuals with known diabetes mellitus. *(Created from data in ES Ford et al: J Diabetes 2:1753, 2010.)*

Cardiovascular Disease

Individuals with the metabolic syndrome are twice as likely to die of the cardiovascular disease as those who do not, and their risk of an acute myocardial infarction or stroke is threefold higher the others. The approximate prevalence of the metabolic syndrome among these patients with coronary heart disease (CHD) is 50%, with a high prevalence of ~35% among patients with premature coronary artery disease (before or at age 45) and a particularly high prevalence among women. With appropriate cardiac rehabilitation and changes in lifestyle (e.g., diet control, nutrition, physical activity, weight reduction, and—in some cases—pharmacologic therapy), the prevalence of the syndrome can be reduced

ETIOLOGY

Insulin Resistance

The most accepted and unifying hypothesis to describe the pathophysiology of the metabolic syndrome is insulin resistance, which is caused by an incompletely understood defect in insulin action and its receptors biology. The onset of insulin resistance is heralded by postprandial hyperinsulinemia, which is followed by fasting hyperinsulinemia and ultimately by hyperglycemia then leading to overt diabetes mellitus. An early major contributor to the development of insulin resistance is an overabundance of circulating free fatty

acids . Plasma albumin-bound free fatty acids are derived predominantly from adipose-tissue triglyceride stores released by intracellular lipolytic enzymes in the body. Fatty acids are also derived from the lipolysis of triglyceride rich lipoproteins in tissues by lipoprotein lipase. Insulin mediates both antilipolysis and the stimulation of lipoprotein lipase in adipose tissue. Of note, the inhibition of lipolysis in adipose tissue in the body is the most sensitive pathway of insulin action. Thus, when insulin resistance develops in the body, increased lipolysis produces more fatty acids synthesis, which further decrease the antilipolytic effect of insulin. Excessive fatty acids enhance the substrate availability and create insulin resistance by modifying downstream signaling pathways within the cell. Fatty acids impair insulin-mediated glucose uptake and accumulate as triglycerides in both skeletal and cardiac muscle, whereas increased glucose production and triglyceride accumulation take place within the liver. Leptin resistance has also been raised as a possible pathophysiologic mechanism to explain the metabolic syndrome. Physiologically, leptin reduces the appetite, promotes energy expenditure, and enhances the insulin sensitivity. In addition, leptin may regulate the cardiac and vascular function through a nitric oxide–dependent mechanism that happens in the body. However, when obesity develops, hyperleptinemia ensues, with evidence of leptin resistance in the brain and all other tissues resulting in inflammation, insulin resistance, hyperlipidemia, and a plethora of cardiovascular disorders, such as hypertension, atherosclerosis, CHD, and heart failure that contributes to its morbidity. The oxidative stress hypothesis provides a unifying theory for aging

and the predisposition to the metabolic syndrome. In studies of insulin resistant individuals with the obesity or type 2 diabetes, the offspring of patients with type 2 diabetes, and the elderly, have a defect in mitochondrial oxidative phosphorylation that leads to the accumulation of triglycerides and related lipid molecules in muscle has been identified.

Recently, the gut microbiome has emerged as an important contributor to the development of the obesity and related metabolic disorders, including the metabolic syndrome. Although the mechanism remain uncertain, interaction among genetic predisposition, diet, and the intestinal flora is very important.

Increased Waist Circumference

Waist circumference is an important component of the most recent and frequently applied diagnostic criteria for the metabolic syndrome . However, measuring the waist circumference does not reliably distinguish increases in subcutaneous adipose tissue from those in visceral fat; this distinction requires imaging studies like CT or MRI. With increases in visceral adipose tissue, adipose tissue–derived free fatty acids are directed to the liver. In contrast, increases in abdominal subcutaneous fat release lipolytic products into the systemic circulation and avert more direct effects on hepatic metabolism. Relative increases in visceral versus suncutaneous adipose tissue with increasing waist circumference in Asians and Asian Indians may explain the greater prevalence of the metabolic syndrome in those populations than in African-American men, in whom SC fat predominates than the visceral fat. It

is also possible that the visceral fat is a marker for—but not the source of— the excess postprandial free fatty acids in obesity.

Dyslipidemia.

In general, free fatty acid flux to the liver from the blood stream is associated with increased production of ApoB-containing,triglyceride-rich, very low-density lipoproteins (VLDLs). The effect of insulin on this process is complex, but the hypertriglyceridemia is an excellent marker of the insulin-resistant condition. Not only is the hypertriglyceridemia a feature of the metabolic syndrome, but patients with the metabolic syndrome have elevated levels of ApoCIII carried on VLDLs and the other lipoproteins. This increase in ApoCIII is inhibitory to the lipoprotein lipase, further contributing to hypertriglyceridemia and also associated with more atherosclerotic cardiovascular disease. The other major lipoprotein disturbance in the metabolic syndrome is a reduction in the HDL cholesterol. This reduction is a consequence of changes in HDL composition and metabolism. In the presence of hypertriglyceridemia, a decrease in the cholesterol content of HDL is a consequence of reduced cholesteryl ester content of the lipoprotein core in combination with cholesteryl ester transfer protein– mediated alterations in triglyceride that make the particle small and dense. This change in lipoprotein composition also results in the increased clearance of HDL from the circulation. These changes in HDL have a relationship to the insulin resistance that is

probably indirect, occurring in concert with the changes in triglyceride-rich lipoprotein metabolism. In addition to HDLs, low-density lipoproteins(LDLs) are modified in composition in the metabolic syndrome. With fasting serum triglycerides at >2.0 mM (~180 mg/dL), there is almost always a predominance small, dense LDLs, which are thought to be more atherogenic than other form of lipoproteins,although their association with hypertriglyceridemia and low HDLs make their independent contribution to cardiovascular disease events difficult to assess. Individuals with hypertriglyceridemia often have increases in cholesterol content of both VLDL1 and VLDL2 subfractions and in LDL particle number. Both of these lipoprotein changes may contribute to atherogenic risk in patients with the metabolic syndrome.

Glucose Intolerance:

Defects in insulin action in the metabolic syndrome lead to the impaired suppression of glucose production by the liver and kidney and reduced glucose uptake and metabolism in insulin-sensitive tissues—i.e., muscle and adipose tissue. The relationship between impaired fasting glucose or impaired glucose tolerance and insulin resistance is well supported by studies of humans, nonhuman primates, and rodents. To compensate for defects in insulin action, insulin secretion and/or clearance must be modified so that the euglycemia is sustained. Ultimately, this compensatory mechanism fails, usually because of

defects in insulin secretion, resulting in progression from impaired fasting glucose and/ or impaired glucose tolerance to overt diabetes mellitus.

Hypertension

The relationship between insulin resistance and hypertension is well established. Paradoxically, under normal physiologic conditions, insulin is a vasodilator with secondary effects on sodium reabsorption in the renal system. However, in the setting of insulin resistance, the vasodilatory effect of insulin is lost but the renal effect on the sodium reabsorption is preserved. Sodium reabsorption is increased in the whites with metabolic syndrome but not in the Africans or Asians. Insulin also increases the activity of the sympathetic nervous system, an effect that may be preserved in the setting of the insulin resistance. Insulin resistance is characterized by the pathway specific impairment in phosphatidylinositol-3-kinase signaling (PI3). In the endothelium, this impairment may cause an imbalance between the production of nitric oxide and the secretion of endothelin 1, with a consequent decrease in blood flow. Although these mechanisms are provocative, the evaluation of insulin action by measurement of fasting insulin levels or by the homeostasis model assessment shows that the insulin resistance contributes only partially to the increased prevalence of hypertension in the metabolic syndrome. Another possible mechanism underlying hypertension in the metabolic syndrome is the vasoactive role of perivascular adipose tissue. Reactive oxygen species released by NADPH oxidase impair endothelial function and result in local

vasoconstriction. Other paracrine effects could be mediated by theleptin or other proinflammatory cytokines released from adipose tissue, such as tumor necrosis factor alpha. Another consequence of insulin resistance is hyperuricemia and is commonly observed in the people with metabolic syndrome. There is growing evidence not only that the uric acid is associated with hypertension but also that reduction of uric acid normalizes blood pressure in hyperuricemic adolescents with the hypertension. The mechanism appears to be related to an adverse effect of uric acid on nitric acid synthase in the macula densa of the renal tubules in the kidney and its stimulation of the renin-angiotensin aldosterone system.

Proinflammatory Cytokines:

The increases in proinflammatory cytokines—including the interleukins 1, 6, and 18; resistin; tumor necrosis factor alpha; and the systemic biomarker C-reactive protein—reflect overproduction by the expanded adipose tissue mass. Adipose tissue–derived macrophages may be the primary source of the proinflammatory cytokines locally and in the systemic circulation. It remains unclear, however, how much of the insulin resistance is caused by the paracrine effects of these cytokines and how much by the endocrine effects are unknown.

Adiponectin

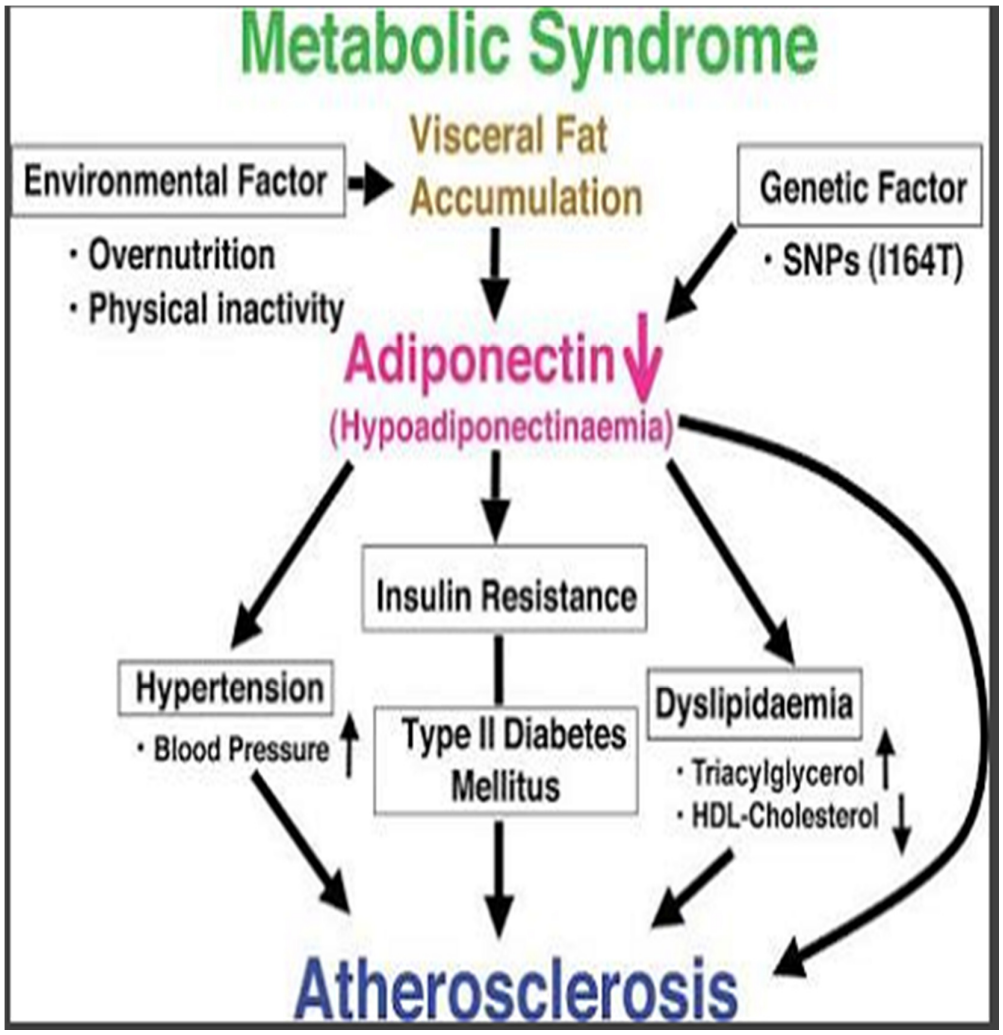
Adiponectin is an anti-inflammatory cytokine produced exclusively by the adipocytes. Adiponectin enhances the insulin sensitivity and inhibits many steps in the inflammatory process. In the liver, the adiponectin inhibits the expression of gluconeogenic enzymes and the rate of glucose production. In muscle, adiponectin increases glucose transport and enhances fatty acid oxidation, partially through the activation of AMP kinase. Adiponectin levels are reduced in the metabolic syndrome. The relative contributions of the adiponectin deficiency and overabundance of the proinflammatory cytokines are unclear.

CLINICAL FEATURES

Symptoms and Signs

The metabolic syndrome typically is not associated with the symptoms. On physical examination, waist circumference may be increased and the blood pressure is elevated. The presence of either or both of these signs should prompt the clinician to search for other biochemical abnormalities that may be associated with the metabolic syndrome. Less frequently, lipoatrophy or acanthosis nigricans, xanthomas are found on the examination. Because these physical findings characteristically are associated with severe insulin resistance, other components of the metabolic syndrome should be expected.

ACTION OF ADIPONECTIN



Associated Diseases

CARDIOVASCULAR DISEASE

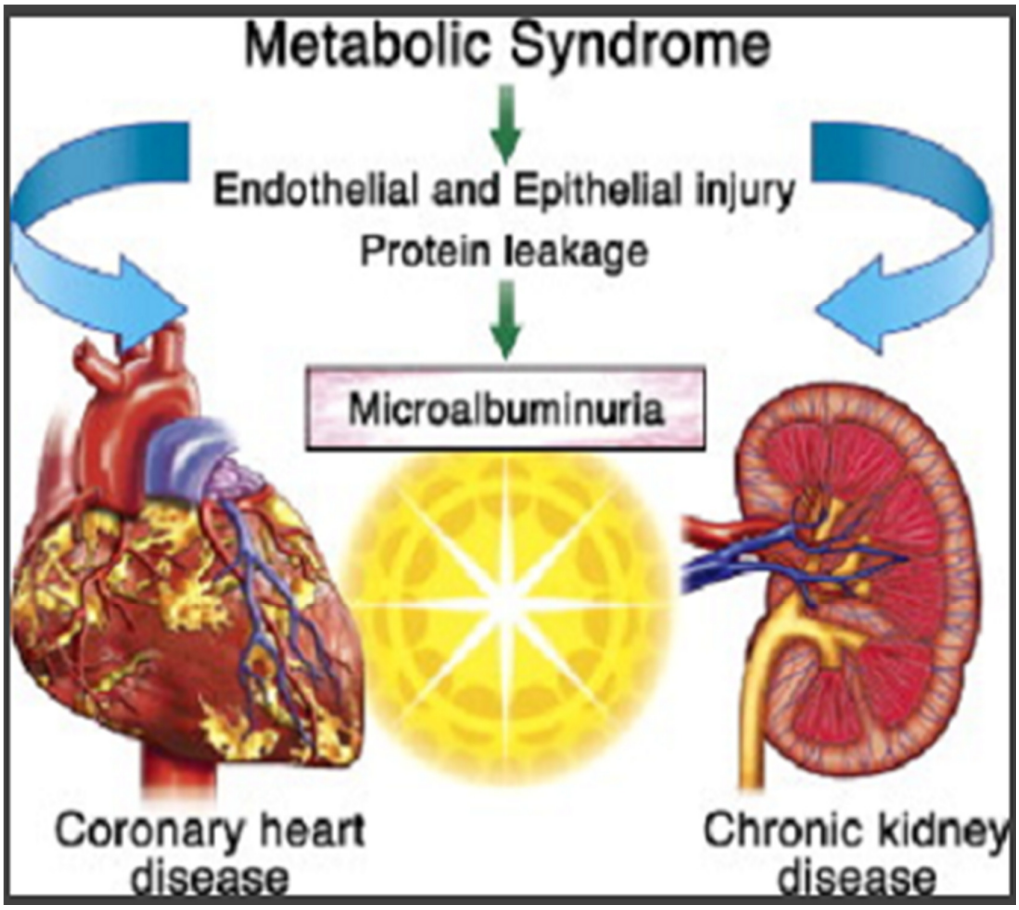
The relative risk for the new onset CVD in patients with the metabolic syndrome who do not have diabetes averages 1.5–3 fold risk. However, an 8-year follow-up of middle aged participants in the Framingham offspring Study documented that the population-attributable CVD risk in the metabolic syndrome was 34% among men and only 16% among women in the study. In the same study, both the metabolic syndrome and diabetes predicted ischemic stroke, with greater risk among patients with the metabolic syndrome than among those with diabetes alone (19% vs. 7%) and a particularly large difference among the women (27% vs. 5%). Patients with the metabolic syndrome are also at increased risk for the peripheral vascular disease. overall, the risk for type 2 diabetes among patients with the metabolic syndrome is increased three- to fivefold than others. In the Framingham Offspring Study's 8-year follow-up of middle-aged participants, the population-attributable risk for developing type 2 diabetes was 62% among men and 47% among the women.

Other Associated Conditions

In addition to the features specifically associated with the metabolic syndrome, other metabolic alterations accompany the insulin resistance. Those alterations include increases in the ApoB and ApoCIII, uric acid level , prothrombotic factors (fibrinogen, plasminogen activator inhibitor 1), serum viscosity, asymmetric dimethylarginine, homocysteine, white blood cell count,

proinflammatory cytokines, C-reactive protein, microalbuminuria, nonalcoholic fatty liver disease and/or nonalcoholic steatohepatitis, polycystic ovary syndrome, and obstructive sleep apnea.

METABOLIC SYNDROME AND MICROALBUMINURIA



NONALCOHOLIC FATTY LIVER DISEASE

Fatty liver is a relatively common condition, affecting 25–45% of the U.S. population.

However, in the nonalcoholic steatohepatitis, the triglyceride accumulation and the inflammation coexist. Nonalcoholic steatohepatitis is now present in the 3–12% of the population of the United States and other Western countries. Of patients with the metabolic syndrome, ~25–60% have nonalcoholic fatty liver disease and up to 35% have nonalcoholic steatohepatitis. As the prevalence of overweight/obesity and the metabolic syndrome increases, nonalcoholic steatohepatitis may become one of the more common causes of end-stage liver disease and hepatocellular carcinoma among the study population.

HYPERURICEMIA

Hyperuricemia reflects defects in insulin action on the renal tubular reabsorption of uric acid in the renal system and may contribute to hypertension through its effect on the endothelium in the blood vessels . An increase in asymmetric dimethylarginine, an endogenous inhibitor of nitric oxide synthase, also relates to endothelial dysfunction. In addition, the microalbuminuria may be caused by altered endothelial pathophysiology in the insulin-resistant state of the body.

POLYCYSTIC OVARY SYNDROME

Polycystic ovary syndrome is highly associated with the insulin resistance (50–80%) and the metabolic syndrome, with a prevalence of the syndrome between

40%and 50%. Women with polycystic ovary syndrome are two to four times more likely to have the metabolic syndrome than are women without polycystic ovary syndrome and its manifestation.

OBSTRUCTIVE SLEEP APNOEA

Obstructive sleep apnea is commonly associated with obesity, hypertension, increased circulating cytokines, impaired glucose tolerance, and insulin resistance. With these associations, it is not surprising that individuals with obstructive sleep apnea frequently have the metabolic syndrome. Moreover, when the biomarkers of insulin resistance are compared between the patients with obstructive sleep apnea and the weight-matched controls, insulin resistance is found to be more severe in those with apnea. Continuous positive airway pressure treatment improves insulin sensitivity in patients with obstructive sleep apnea and its symtoms .

AIMS AND OBJECTIVE :

1.TO STUDY THE ASSOCIATION BETWEEN METABOLIC SYNDROME AND ACUTE CORONARY SYNDROME

2.TO STUDY THE PREVALANCE OF METABOLIC SYNDROME IN ACUTE CORONARY SYNDROME

REVIEW OF LITERATURE

Metabolic syndrome

Metabolic syndrome is defined as a clustering of cardiovascular risk factors in an individual which predisposes the person to a greater risk of developing the type 2 diabetes mellitus and the cardiovascular disease.

It was first coined as syndrome X in the year 1988.

Main feature of metabolic syndrome includes the insulin resistance.

Criteria for diagnosis

1) International disease federation
2) WHO criteria
3) National cholesterol education panel ATP III guidelines.

Nomenclature

Other names for metabolic syndrome are the following

Syndrome X

Metabolic syndrome X

Pluri metabolic syndrome

Insulin resistance syndrome

"deadly quartet,"

Hyper triglyceridemic waist.

Reaven's Syndrome

HISTORY OF METABOLIC SYNDROME

The term "metabolic syndrome" dates back to the late 1950s, but came into common usage in late 1970s to describe various associations of risk factors with the diabetes that had been noted as early as the 1920s

In 1947 Marseilles physician Dr. Jean Vague, observed that the upper body obesity appeared to predispose to diabetes, atherosclerosis, gout and calculi.

Avogadro, Crepaldi and his co-workers described the six moderately obese patients with diabetes, hypercholesterolemia, and marked hypertriglyceridemia all of which improved when the patients were put on a hypocaloric, low-carbohydrate diet.

In 1977 and 1978, Gerald B. Phillips developed the concept that the risk factors for myocardial infarction concur to form a "constellation of abnormalities" (i.e., glucose intolerance, hyperinsulinemia ,hypercholesterolemia, hypertriglyceridemia, and hypertension) that is associated not only with heart disease but also with aging, obesity and other clinical states. He suggested that there must be an underlying linking factor, the identification of which could lead to the prevention of cardiovascular disease; he hypothesized that this factor was the sex hormones.

In 1988, Gerald Reaven[(1)] reintroduced the concept of syndrome X for the clustering of cardiovascular risk factors like hypertension, glucose intolerance, high triglycerides, and low HDL cholesterol concentrations. The syndrome is however, the much older, having been already observed in 1923 by the Kylin,

who described the clustering of hypertension, hyperglycemia, and the gout as a syndrome.

In 1998, WHO proposed a unifying definition for the syndrome and chose to call it the metabolic syndrome rather than the insulin resistance syndrome. This name was chosen primarily because it was Not considered established that insulin resistance was the cause of all the components of the syndrome.

The metabolic syndrome (syndrome X, insulin resistance syndrome) consists of a constellation of metabolic abnormalities that confer increased risk of cardiovasculardisease (CVD) and diabetes mellitus (DM). The criteria for the metabolic syndrome have evolved since the original definition by the World Health Organization in 1998, reflecting the growing clinical evidence and analysis by a variety of consensus conferences and professional organizations. The major features of the metabolic syndrome include the central obesity, hypertriglyceridemia, low HDL cholesterol, hyperglycemia, and hypertension.

Epidemiology

Prevalence of the metabolic syndrome varies across the world, in part reflecting the age and ethnicity of the populations in the globe studied and the diagnostic criteria applied. In general, the prevalence of metabolic syndrome increases with the age. The highest recorded prevalence worldwide is in Native Americans ,with nearly around 60% of women ages 45–49 years and 45% of men ages 45–49years meeting National Cholesterol Education Program, Adult Treatment Panel III (NCEP:ATPIII) criteria. Based on data from the National

Health and Nutrition Examination Survey (NHANES) III[2], the age-adjusted prevalence of the metabolic syndrome in the United States is around 34% for men and 35% for the women. In France, a 30–64-year-old cohort shows a <10% prevalence for each gender, although 17.5% are affected in the 60–64 years of age. Greater industrialization worldwide is associated with rising rates of obesity, which is anticipated to dramatically increase in the prevalence of the metabolic syndrome, especially as the population ages. Moreover, the rising prevalence and the severity of obesity in children is initiating features of the metabolic syndrome in a younger population.

Definitions of Metabolic syndrome

There are various definitions for metabolic syndrome. The widely used definitions are

I. WORLD HEALTH ORGANISATION (WHO)[3]

Clinical Measure	**WHO (1988)**
Insulin resistance	impaired glucose tolerance, Impaired fasting glucose , T2DM, or lowered Insulin sensitivity plus Any 2 of the following
Body weight	Men: waist to hip ratio>0.90 Women: waist to hip ratio>0.85

	And/ or BMI>30 kg/ sq. m
Lipid	TG >=150 mg/dL
	HDL cholesterol <40 mg/dL
	for the men,
	<50 mg/dL for the women
Blood pressure	>=140/90 mmHg.
Glucose	IGT,IFG or T2DM
OTHER	**microalbuminuria (Urinary albumin to creatinine** ratio: 30 mg per gram , or albumin excretion rate: 20mcgper minute)

II. INTERNATIONAL DIABETIC FEDERATION[4]

Clinical Measure	**IDF (2005)**
Insulin resistance	None
Body weight	Increased waist circumference (population specific)Plus any 2 of the following criteria
Lipid	TG >=150 mg/dL or on R/
	HDL cholesterol <40 mg/dL
	for men,
	<50 mg/dL for women or on R/

Blood pressure	>=130/85 mmHg or on R/
Glucose	>=100 mg/dL(including diabetes)

III. THE ADULT TREATMENT PANEL[5] III OF THE NATIONAL CHOLESTEROL EDUCATION PROGRAM (2001, 2005)

It defined the diagnosis as three or more of the following five

1. Increased waist circumference (>=102 cm in men and >=88 cm inwomen)
2. Elevated triglycerides (>=150 mg/dL or 1.7 mmol/l)
3. Decreased HDL cholesterol (<40 mg/dL for men, <50 mg/dL for women)
4. Blood pressure above 130/85 or active treatment for hypertension
5. Glucose levels above 100 mg/dL or active treatment for hyperglycemia

IV. AMERICAN HEART ASSOCIATION , NATIONAL HEART , LUNG AND BLOOD INSTITUTE[6], JULY 2005 SCIENTIFIC STATEMENT

Metabolic syndrome was defined according to the AHA/NHLBI statement and maintaining NCEP ATP III1 criteria with minor modifications. Patients received a diagnosis of metabolic syndrome if they had any 3 of the following 5 criteria:

1. Abdominal obesity (waist circumference in men >102 cm and in women >88cm for western population and > 90 cm in men and > 80 cm in women of Asian origin)

2. High triglyceride levels >=150mg/dL

3. Low HDL Cholesterol level <40 mg/dL in men and <50 mg/dL in women

4. High blood pressure (treated hypertension, and systolic blood pressure >=130mm Hg, or diastolic blood pressure >= 85 mm Hg)

5. Fasting glucose >= 100 mg/dL or on treatment for diabetes mellitus. In accordance with the 2003 recommendation from the American Diabetes Association[7], in the last three definitions of IDF, Adult Treatment Panel III of the National Cholesterol Education Program (2001, 2005) and AHA/NHLBI statement the value of impaired fasting glucose was reduced from 110 mg/Dlto 100 mg/dL.When the waist circumference is 90 cm or more in men or 80 cm or more in women, the term abdominal obesity can be applied. The advantage of measuring waist circumference is that an excess abdominal fat is correlated more closely with the presence of metabolic risk factors than total body fat.

GENETICS

A "thrifty genotype hypothesis" implicates the evolutionary selection of metabolic genes in the development of the metabolic syndrome in the setting of the modern environment of physical inactivity and dietary excess. Family studies suggest a complex but significant genetic basis to the individual components of the metabolic syndrome. However, identifying a genetic profile that defines an increased risk of developing a complex disease trait, such as the metabolic syndrome or the atherosclerosis, remains difficult to elucidate.

Concept of genes predisposing to metabolic syndrome

Mutations in the PPAR gene that disrupt the function of the protein causes severe IR,(savage et al 2003)[8] ,Dyslipidemia and the Hypertension

Calpain 10 gene is the important in modification and processing of proteins in the cell.(sang et al)[9].

Variants in calpain gene alter the risk to Type 2 DM. Variants in SUR & kir 6.2 cause rare a diabetes related disorders & predispose to the Type 2 DM[10].

Mutations in HNF1 . HNF-4 and rarely in GCK gene cause MODY.

Biomarkers of metabolic syndrome[11]

Lipid and Lipoproteins	**Low density lipoprotein**	**Vascular injury**
Adipokines	Leptin Adiponectin Resistin	Modulation of insulin sensitivity . Anti-inflammatory action. Impairment of the glucose tolerance.
Inflammatory Markers	C-reactive protein TNF alpha receptor 2 Interleukin -6 Interleukin-8	Endothelial dysfunction Insulin resistance Athero thrombosis.
Chemokines	Monocyte chemotactic protein	Neutrophils attraction to The endothelium.
Haemostatic markers	Plasminogen activator inhibitor 1	Induction of cell the adhesion molecule expression. Insulin resistance.

Risk Factors

Overweight / Obesity

Central adiposity is a key feature of the syndrome, reflecting the fact that the syndrome's prevalence is the driven by the strong relationship between waist circumference and the increasing adiposity. However, despite the importance of obesity, patients who are normal weight may also be insulin-resistant and have the metabolic syndrome.

Sedentary Lifestyle

Physical inactivity is the most important predictor of cardiovascular events and related mortality. Many components of the metabolic syndrome are associated with a sedentary lifestyle ,including increased subcutaneous adipose tissue in (predominantly central); reduced HDL cholesterol; and a trend toward the increased triglycerides, high blood pressure, and high blood glucose levels in the genetically susceptible. Compared with individuals who watched television or the videos or used their computer <1 hour daily, those who carried out these behaviors for >4hours daily have a twofold increased risk of the metabolic syndrome.

PATHOPHYSIOLOGY -MECHANISTIC LINKS BETWEEN COMPONENTS

INSULIN RESISTANCE

Insulin resistance per se is independently an atherogenic phenomena. Insulin resistance is the pathophysiological process underlying the clustering of cardiovascular risk factors in the metabolic syndrome[12,13]. In prospective studies, the presence of insulin resistance is associated with increased ASCVD risk[14]. Some of the risk factors that are hallmark of insulin resistance—for example, abnormal lipid levels, the glucose intolerance, and the high blood insulin levels—appear to provide a fertile ground for the development of serious chronic diseases such as diabetes, heart disease, and fatty liver. For the instance, high blood insulin levels have been linked to the hypertension, while insulin resistance appears to be to promote atherosclerosis.

Multiple metabolic pathways have been proposed to link insulin resistance and the compensatory hyperinsulinemia to the other metabolic risk factors[13,15].

PATHOPHYSIOLOGY OF METABOLIC SYNDROME

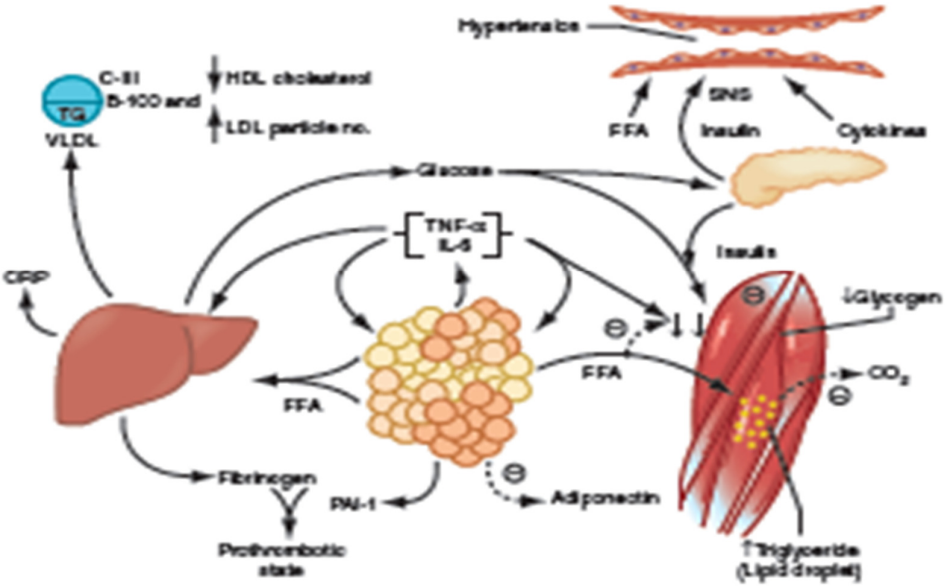


FIGURE 422-2 Pathophysiology of the metabolic syndrome. Free fatty acids (FFAs) are released in abundance from an expanded adipose tissue mass. In the liver, FFAs result in increased production of glucose and triglycerides and secretion of very low density lipoproteins (VLDLs). Associated lipid/lipoprotein abnormalities include reductions in high-density lipoprotein (HDL) cholesterol and an increased low-density lipoprotein (LDL) particle number (no.). FFAs also reduce insulin sensitivity in muscle by inhibiting insulin-mediated glucose uptake. Associated defects include a reduction in glucose partitioning to glycogen and increased lipid accumulation in triglyceride (TG). The increase in circulating glucose, and to some extent FFAs, increases pancreatic insulin secretion, resulting in hyperinsulinemia. Hyperinsulinemia may result in enhanced sodium reabsorption and increased sympathetic nervous system (SNS) activity and contribute to hypertension, as might higher levels of circulating FFAs. The proinflammatory state is superimposed and contributory to the insulin resistance produced by excessive FFAs. The enhanced secretion of interleukin 6 (IL-6) and tumor necrosis factor α (TNF-α) produced by adipocytes and monocyte-derived macrophages results in more insulin resistance and lipolysis of adipose tissue triglyceride stores to circulating FFAs. IL-6 and other cytokines also enhance hepatic glucose production, VLDL production by the liver, hypertension and insulin resistance in muscle. Cytokines and FFAs also increase hepatic production of fibrinogen and adipocyte production of plasminogen activator inhibitor 1 (PAI-1), resulting in a prothrombotic state. Higher levels of circulating cytokines stimulate hepatic production of C-reactive protein (CRP). Reduced production of the anti-inflammatory and insulin-sensitizing cytokine adiponectin is also associated with the metabolic syndrome. *(Modified from RH Eckel et al: Lancet 365:1415, 2005.)*

This is true for many individuals of the South Asian ethnicity[16,17]. Although insulin resistant individuals need not be clinically obese, they have an abnormal fat distribution that is characterized by predominant upper body fat.

Asymmetric dimethylarginine (ADMA), a naturally occurring molecule , is increased in the metabolic syndrome . It inhibits the synthesis of nitric oxide, which is a potent dilator of blood vessels. ADMA also increases the binding of the white blood cells to the endothelial lining of arteries, which may contribute to the atherosclerosis.

Indices of insulin resistance predict atherosclerosis and cardiovascular events independent of other risk factors including fasting glucose and lipid levels[18]. Many subjects with the normal fasting glucose levels have insulin resistance[12].The hyperinsulinemic clamp is considered to be the gold standard to define insulin sensitivity but requires prolonged insulin infusion and repeated blood sampling. Surrogate measures of insulin sensitivity, including the Homeostasis Model Assessment (HOMA) and Quantitative Insulin Sensitivity Check Index(QUICKI), have been developed that can be applied to single measurements of fasting insulin and glucose. These surrogates are useful in defining the MetSyn and in predicting the development of the cardiovascular disease and type 2 diabetes mellitus[18,19].

Insulin resistance is thought to be the contributor to the accumulation of fatty deposits in the liver. Insulin resistance also has been implicated in polycystic ovary syndrome[20]and nonalcoholic steatohepatitis (NASH).

Innate immunity and inflammation play a role in the development of insulin resistance and predict the development of type 2diabetes mellitus[21,22]. Thus, the pathophysiology of insulin resistance and atherosclerotic cardiovascular events may have a common proximal inflammatory basis.

DYSGLYCEMIA

In cross-sectional and prospective studies, fasting and postprandial glucose an insulin concentrations are positively correlated to the metabolic syndrome. The increase in insulin concentrations is paralleled by a decrease in insulin sensitivity. Decreased insulin sensitivity leads to defects in the ability of the insulin to inhibit hepatic glucose production and to stimulate glucose uptake in peripheral tissues and thereby leading to the hyperglycemia.

Increased FFA concentrations and resistance to the antilipolytic effect of insulin may contribute to the worsening of hyperglycemia[23] because of the multiple interactions between the FFA and glucose metabolism both in the liver and also in skeletal muscle. A variety of mechanisms to explain how elevated plasma glucose may promote the atherosclerosis are postulated[24].

A variety of mechanisms have been proposed whereby hyperglycemia might promote the atherosclerosis [24]. Examples include nonenzymatic glycosylation of lipids and the proteins, pathogenic effects of advanced glycation products,increased oxidative stress free radicals , activation of protein kinase C, and microvascular disease of the vasa vasorum of the coronary arteries in the heart.

OBESITY AND ABDOMINAL OBESITY

Obesity is related to insulin resistance[25,26] Obesity is associated with impaired insulin stimulation of glucose uptake and defect in the ability of insulin to inhibit endogenous glucose production and lipolysis in the adipose tissue of the body. These defects will appear more severe in individuals with android (abdominal fat distribution) than the gynoid obesity.

Upper-body obesity correlates strongly with the insulin resistance. Excess visceral fat deposition than the subcutaneous fat deposition is strongly associated with the insulin resistance. Excess subcutaneous abdominal (or truncal) fat also carries a significant association with the insulin resistance[27-32].An interesting feature of upper-body obesity is a high release of nonesterified fatty acids from adipose tissue in to the blood stream[33,34]; this contributes to accumulation of lipid in sites other than adipose tissue. Ectopic lipid accumulation in muscle and liver seemingly predisposes to insulin resistance[35]and dyslipidemia[36].

The foremost physical consequence of obesity is atherosclerotic cardiovascular disease (ASCVD)[37,38]. The majority of obese persons who develop ASCVD typically have metabolic syndrome.

Body mass index is relatively insensitive indicator for the metabolic and cardiovascular complications of obesity, as compared with measures of central or abdominal adiposity[39]. Waist circumference reflects both abdominal subcutaneous adipose tissue(SAT) and abdominal visceral adipose tissue

(VAT) and is the general index of central(trunk) fat mass. So, waist circumference is preferred more for measuring the abdominal obesity. VAT has been proposed as the major determinant of metabolic and cardiovascular complications of obesity[40].

Our understanding of the relation between obesity and metabolic risk factors is growing rapidly. This understanding is based on the discovery of multiple products released from adipocytes like [41].

Nonesterified fatty acids (NEFAs)

Inflammatory cytokines

PAI-1

Adiponectins

Leptins

Resistins

Circulating cytokines have systemic effects, *i.e*. promoting insulin resistance in the muscle[42], increased synthesis of the acute-phase reactants in the liver (CRP and fibrinogen), or activation of macrophages in atheromatous plaques[43].

Excessive influx of NEFAs into the muscle leads to insulin resistance. Randle et al[44] postulated that the excess fatty acids in muscle inhibit the glucose oxidation (glucose-fatty acid cycle). Recent research suggests that the muscle levels of diacylglycerol are raised, which stimulates the serine phosphorylation of the insulin receptors and thereby inhibits normal insulin signaling. Other mechanisms also may play a role in insulin resistance in the muscle[45].

Fat accumulation in the liver seemingly to produces insulin resistance as it does in muscle also. Reduction in insulin action in liver allows for enhanced gluconeogenesis and increased hepatic glucose output.

Hypotheses have been developed to link higher NEFA levels to higher blood pressures[46]. Accumulation of fat in the liver has been reported to be associated with the increased hepatic synthesis of PAI-1, fibrinogen, and inflammatory cytokines, the key mediators of the prothrombotic and proinflammatory states[47].

Adipose tissue synthesizes PAI-1. A fatty liver may be the another source of PAI-1 production.The resulting high PAI-1 levels in the obese persons together with the high plasma fibrinogen observed in such persons contributes to a prothrombotic state.

Adiponectin[48] is reported to have an antiinflammatory and antiatherogenic properties. Obese persons generally have low levels of adiponectin and hence may be deprived of its protective effects against the metabolic syndrome.

Leptin also may play a systemic role beyond being an adipose tissue-derived appetite suppressant substance. This hormone has been reported to have a beneficial effect on the liver to protect against the fatty liver[49,50]. Its mechanism may be to enhance fatty acid oxidation in the liver. Finally, resistin is an adipose tissue-derived hormone that seemingly opposes the action of insulin in the body[51].

DYSLIPIDEMIA

Dyslipidemia is a hallmark of the metabolic syndrome and is characterized by the elevated triglycerides (TG) and low levels of HDL-C. Increased fat in the liver provides a stimulus for the increased formation and the secretion of very LDL (VLDL) particles. The result is higher serum levels of triglyceride, apo B, and small LDL particles. High serum triglycerides reduce HDL-cholesterol concentrations through exchange of VLDL triglycerides with HDL cholesterolesters lipoproteins.

HYPERTRIGLYCERIDEMIA

Influx of excess NEFAs into the liver increases the triglyceride content of the liver (fatty liver)[52]. Increased flux of free fatty acids from the periphery to the liver in the insulin-resistant state drives hepatic TG synthesis, which in turn promotes the assembly and secretion of TG-containing VLDL.

Insulin normally suppresses the production of VLDL particles from the liver by directly inhibiting the assembly and production of VLDL particles[53]. In insulin resistance this action of Insulin is lost leading to the increase in serum triglycerides[54].Under hypertriglyceridemic conditions, there is an excessive exchange of cholesterol esters and triglyceride-rich lipoproteins, mediated by the cholesterol ester transfer protein.

LOW HDL CHOLESTEROL

Metabolic syndrome is associated with the low HDL cholesterol. HDL particles become enriched with the triglycerides[55] and act as good substrate for hepatic lipase which now removes HDL particles at an accelerated rate than thought before. This is mediated by mediated by the cholesteryl ester transfer protein. Subnormal activity of lipoprotein lipase may further decrease level of HDL cholesterol in the blood. Activation of innate immunity offers a potential unifying pathophysiology for insulin resistance and dyslipidemia in the metabolic syndrome than thought before. In animal models, activation of innate immunity leads to changes in lipoproteins ,enzymes, transfer proteins, and receptors with an increase in atherogenic lipoprotein particle molecule. One possible contributor to the changes in HDL during inflammation is the increased production of lipases that act on HDL phospholipids, thus reducing the lipid content of HDL and promoting its catabolism in the body.

A low HDL level is another characteristic of atherogenic dyslipidemia. As an risk predictor, a low HDL rivals an elevated total apo B lipoprotein (or VLDL+LDL cholesterol). This fact has led to the concept that HDL is intimately involved in the atherogenic process in the body. The theories abound as to the mechanisms whereby HDL is antiatherogenic are enhanced reverse cholesterol transport, antiinflammatory properties, ability to protect against the LDL modification. Although HDL in fact may be directly antiatherogenic and it also is a marker for the presence of other lipid and nonlipid risk factors.

SMALL DENSE LDL PARTICLES

In metabolic syndrome LDL particles are smaller and denser than normal. Small dense LDL particles are known to be highly atherogenic [56] than others and provide aplausible link between the insulin resistance and the cardiovascular disease.

The increase in the triglyceride content of LDL particles[57] makes them a better substrate for the hepatic lipase which hydrolyzes triglycerides in the LDL particles and so decrease their size.

High levels of the circulating oxidised LDL, which is increased in metabolic syndrome are associated with a greater disposition to atherothrombotic coronary disease[58]. A theory widely held is that smaller LDL particles are more atherogenic than larger LDLs[59]. Small LDL particles are a surrogate for an increased LDL particle number[60] .

A simple strategy for assessing the sum of the atherogenic particles is measurement of either LDL+VLDL cholesterol (non-HDL cholesterol) or total apoB . In persons with metabolic syndrome, both LDL+VLDL cholesterol and total apoB typically are elevated. These measurements should be used increasingly both in the risk assessment and as targets of therapy in persons with the metabolic syndrome[61].

HYPERTENSION

The association between the insulin resistance and hypertension is perhaps the most controversial. In insulin resistant patients with essential hypertension , the basal intracellular calcium levels have been shown to be elevated and the

normal ability of insulin to attenuate angiotensin II induced increases in intracellular calcium is blunted in skin fibroblasts in the body[62].

The renal action of insulin is to reabsorb sodium is similar in normo- and also in hypertensive insulin-resistant subjects. Such a preserved action of insulin may contribute to an increase in the blood pressure in hyperinsulinemic individuals[63].

Insulin resistance has been consistently found to correlate with high sodium-lithium counter-transport in the erythrocyte membranes: this is thought to be parallelly increased activity of the sodium hydrogen ion pump in the cell membrane of other tissues ,which could raise the intracellular sodium and calcium concentrations and enhance vascular muscle contractility. Such action could also contribute to the development of hypertension in non-diabetic, insulin resistant subjects.

A higher blood pressure is a strong risk factor for cardiovascular disease (CVD)[64]. Well-known complication of hypertension are CHD, stroke, left ventricular hypertrophy, heart failure, and chronic renal failure. Hypertension is particularly dangerous to the cardiovascular system. This concept supported by the well known Framingham Heart Study[65].

Hyperuricemia

Within the non-diabetic range of glucose tolerance, serum uric acid concentrations are positively correlated with the glucose and insulin concentrations and inversely with the insulin resistance[66].

In normal subjects, insulin acutely reduces the renal clearance of both sodium and uric acid levels[67]. These actions are preserved in insulin resistant states such as obesity, diabetes and essential hypertension and so provide a potential mechanistic link for the clustering of the insulin resistance with hyperuricemia[68].

ALTERATIONS IN COAGULATION, FIBRINOLYSIS AND PLATELET FUNCTION

Metabolic syndrome is also associated with a proinflammatory/prothrombotic state that includes the elevated levels of the C-reactive protein, endothelial dysfunction ,hyperfibrinogenemia, increased platelet aggregation, increased the levels of plasminogenactivator inhibitor 1, elevated uric acid levels and microalbuminuria Pro-coagulant changes such as impaired fibrinolysis and increased levels of the PAI-I and defects in platelets function are frequently associated with insulin resistance. PAI-I, an inhibitor of fibrinolysis, is elevated in obesity associated insulin resistance[69].

Coagulation and the fibrinolytic abnormalities cause endothelial dysfunction, which in turn is involved in the atherogenic process[70].

CHANGES IN INFLAMMATORY MARKERS

IL-6 , the main regulator of the synthesis of C-reactive protein in the liver[71] is increased in metabolic syndrome. Upto one third of the circulating IL-6 originate from the subcutaneous and visceral adipose tissue depots and

circulating levels are increased in obese subjects[72].Recently, this syndrome has been noted to be associated with the state of chronic, low-grade inflammation[73,74]. It is of the interest that obese persons[75] and particularly those with the metabolic syndrome[76] also have the elevated levels of CRP

MICROALBUMINURIA

The mechanisms underlying the clustering of insulin resistance and microalbuminuria are poorly understood even with large studies. Insulin has been shown to increase urinary excretion of albumin and protein markers of proximal tubular function in diabetic patients but not in nondiabetic individuals[77]. Microalbuminuria may also be a sign of preclinical endothelial or vascular damage[78].

ABNORMALITIES IN THE AUTONOMIC NERVOUS SYSTEM

In insulin resistant subjects, insulin can enter the hypothalamus and other parts of the brain, where insulin receptors are expressed at high levels, and it acts centrally to stimulate the sympathetic nervous system[79]. Insulin also regulates the autonomic control of heart rate by the decreasing vagal tone, and increasing sympathetic drive[80].

ACUTE MYOCARDIAL INFARCTION AND METABOLIC SYNDROME

In prospective epidemiologic studies, hyperinsulinemia is an independent risk factor for the devolepment ofCHD in the non-diabetic men after adjusting for body weight, blood pressure and dyslipidemia[81].This study also reveals that the patients with an AMI and no previous diagnosis of diabetes mellitus have a high prevalence of insulin resistance[82] . There has been consistent relationship of metabolic syndrome with prevalent of MI and stroke[83].

In men participating in the West of Scotland Coronary prevention Study, the insulin resistance syndrome is defined as according to NCEP criteria increased the risk for the CHD event by 1.76 fold. Men with the four to five features of the syndrome had a 3.7 fold increase in risk for the CHD.

OTHER MARKERS OF METABOLIC SYNDROME AS PREDICTORS OF CARDIOVASCULAR DISEASE

C-reactive protein has predicted the cardiovascular disease independent of other risk Factors .Hyperuricemia is associated with increased mortality from all causes of the cardiovascular disease in the NHANES I2 epidemiologic survey in women but not in men. The PAI-I has been found predictive for cardiovascular disease in several studies[84]. Microalbuminuria increased the relative risk of CHD death eightfold and of all CHD events threefold even after adjusting for gender, smoking, blood pressure and HDL cholesterol[85].

All these predictors of the cardiovascular disease namely CRP, hyperuricemia, PAI-I and microalbuminuria are strongly associated with metabolic syndrome.

MANAGEMENT OF METABOLIC SYNDROME

Metabolic syndrome is the secondary target for reducing cardiovascular events. Smoking cessation, lowering the levels of LDL-C, and blood pressure management are primary target for risk reduction. Lifestyle modifications are the initial therapies recommended for treatment of metabolic syndrome. If lifestyle change is not a sufficient, then drug therapies may be indicated for the management. To date, there is insufficient evidence for primary use of the drugs that target the underlying causes of metabolic syndrome.

LIPOPROTEINS:

Lipoproteins are the complexes of lipids and proteins that are essential for the transport of cholesterol, triglyceride and fat soluble vitamins. It contains a core of hydrophobic lipids triglycerides and cholestryl esters surrounded by hydrophilic lipids phospholipids and unesterified cholesterol and proteins that interact with the body fluids[86].

Plasma lipoproteins are divided into five major classes based on their relative density.

Chylomicrons

- Very low density lipoproteins
- Intermediate density lipoproteins

 Low density lipoproteins

 High density lipoproteins.

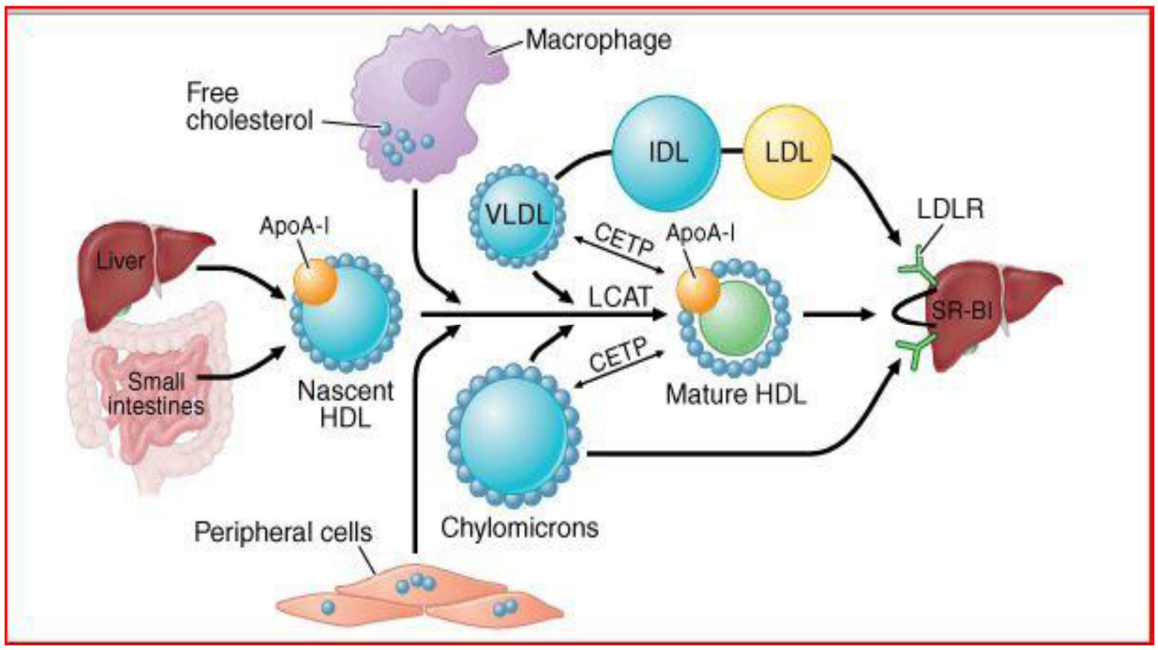
HDL is the smallest and most dense lipoprotein, chylomicron and VLDL are the largest and least dense lipoprotein.

The proteins associated with lipoproteins are called apolipoproteins they are required for the assembly structure and function of lipoproteins.

APO A1 synthesized in the liver and intestine is found in all HDL particles.

APO B 48 –contains chylomicrons

APO B 100-VLDL, IDL or LDL.



METABOLISM OF LIPO PROTEINS

Transport of dietary lipids

Exogenous pathway[87]

Dietary triglycerides are hydrolyzed by lipoprotein lipases within the intestinal lumen and emulsified with bile acids.

Cholesterol and retinol are esterified to form the cholestryl esters and retinyl esters.

Longer chain fatty acids are incorporated into triglycerides and packaged with APO B 48 cholestryl esters, phospholipids and cholesterol to form the chylomicrons.

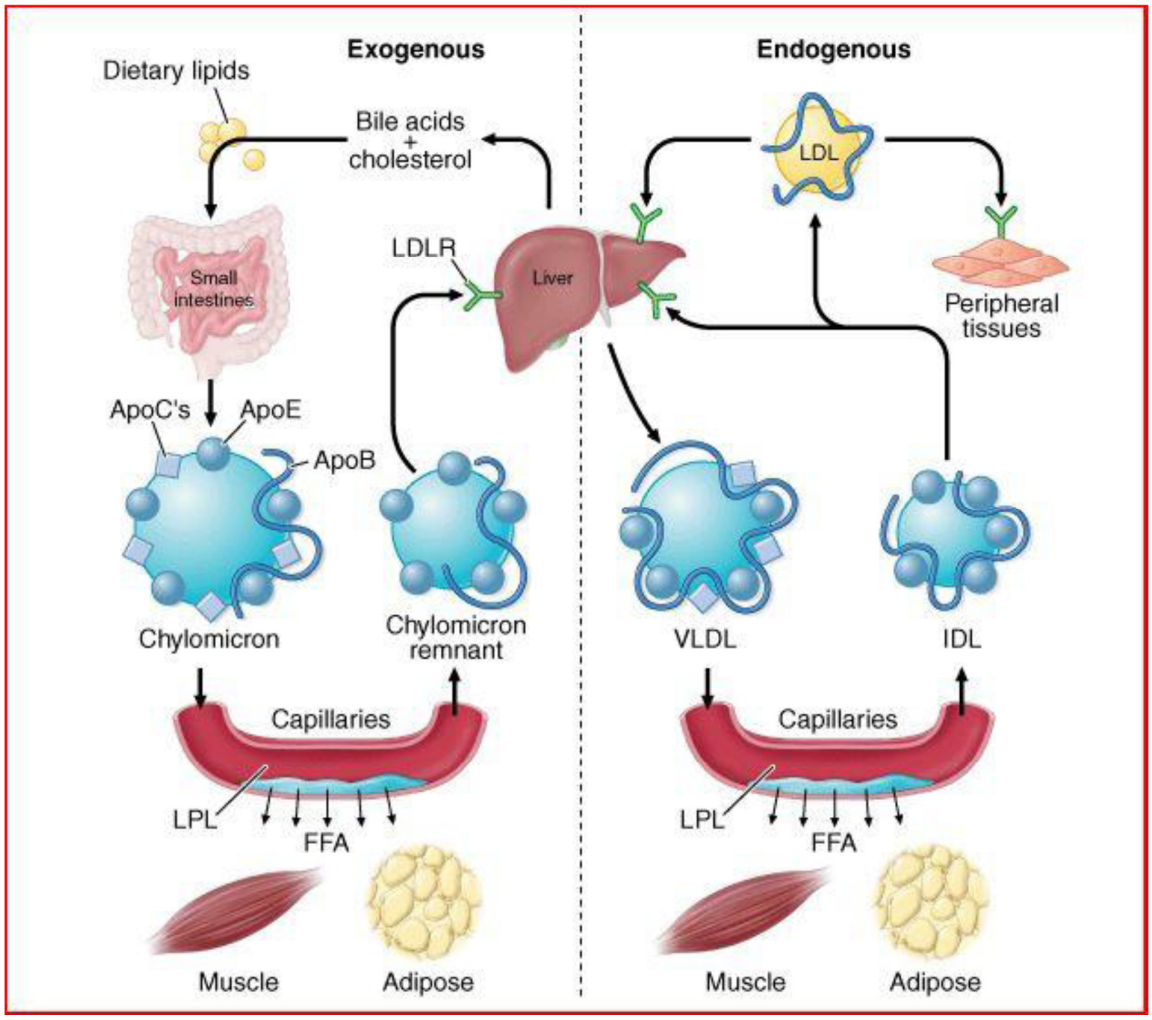
Nascent chylomicrons are secreted into intestinal lymph and delivered via thoracic duct to systemic circulation.

They become chylomicrons when the nascent particles combine with apo CII and apo E derived from HDL.

The enzyme lipoprotein lipase present in capillary walls of adipose tissue cardiac and skeletal muscle hydrolyses the triacylglycerol present in the chylomicrons and releases the free fatty acids and the glycerol.

Lipoprotein lipase is activated by the apo CII.

The chylomicron remnants are taken up by the receptors present on the hepatocytes of the liver.



TRANSPORT OF LIPO PROTEINS

Endogenous pathway[88]

 VLDL particles resemble the chylomicrons in protein composition but contain the APO B 100.

 Packaging of the hepatic triglycerides with other components of the nascent VLDL particle require the action of MTP.

 Triglycerides are formed due to the esterification of the long chain fattyacids in the liver.

 After the secretion into the plasma VLDL acquires APO CII and APO from the HDL.

 VLDL are also hydrolyzed by lipoprotein lipase especially in the muscle and adipose tissue.

 They lose the APO CII after which IDL is formed.

 It loses the APO E and gets converted to LDL.

 LDL contains high cholesterol and less triacylglycerol.

 the cholestrol in LDL accounts for over half of the plasma cholesterol in most individuals.

 Approximately 70% of the LDL cholesterol is cleared by LDL receptor mediated endocytosis in the liver.

Investigations to be done in case of metabolic syndrome

 Fasting lipid level

 Fasting glucose

- Liver function test.
- APO B
- High sensitivity –CRPs
- Fibrinogens
- Uric acids
- Sleep study if the obstructive sleep apnea is present
- Testosterone, luteinizing hormone, follicle stimulating hormone in case of polycystic ovary disease.
- Urinary microalbumin.

Treatment of metabolic syndrome

Life style

Weight reduction is the first and foremost approach to this disorder. Recommendations for weight loss is calorie restriction with increased physical activity and behavioural modification[89].

Diet-

500 kcal restriction is adviced daily . carbohydrate restricted diet provide a rapid initial weight loss.

Physical activity

Increase in the physical activity leads to weight reduction. 60-90 min of daily walking activity is required to achieve this goal[90].

Obesity

Weight loss drugs can also be used. Drugs like phentermine and sibutramine, orlistat inhibits fat absorption. bariatric surgery are other and final options[91].

LDL cholesterol

- Diet restricted in the saturated fats.
- HMG COA reductase inhibitors are the first choice of drugs.
- Ezetimibe is second choice.
- Bile acid sequestrants are more effective.
- cholestyramine and cholestipol.
- Nicotinic acid
- Fenofibrates are the other drugs which can also be used.

Triglycerides

Weight reduction

Gemfibrozil or fenofibrate is the drug of choice to lower fasting triglycerides[92].

Other drugs are statins nicotinic acid and omega 3 fatty acid preparations.

HDL cholesterol

Nicotinic acid is the only available drug to raise the HDL cholesterol.

Blood pressure

In patients with metabolic syndrome with diabetes ACE inhibitors or ARB are used[93].

Impaired fasting glucose

Metformin has been showed to reduce the incidence of diabetes. Insulin resistance Both metformin and thiazolidinediones increase insulin sensitivity.

Blood supply of heart

Heart is supplied by two coronary arteries arising from the sinus of ascending aorta.both of which run in the coronary sulcus.

Right coronary artery[94]

Is smaller than the left coronary artery .It arises from the anterior aortic sinus.

Branches

Large branches

Marginal

Posterior inter ventricular

Small branches

Nodal

Right atrial

Infundibular and terminal.

Area of distribution

Right atrium

Ventricles

Greater part of the right ventricle except the area adjoining the anterior interventricular groove.

A small part of the left ventricle adjoining the posterior interventricular groove.Posterior part of interventricular septum.

Whole of the conducting system of the heart except the part of the left branch of AV bundle.

Left coronary artery[95]

Larger than the right coronary artery.arises from the left posterior aortic sinus.

Branches

Large branches

Anterior interventricular

Branches to the diaphragmatic surface of left ventricle.

Diagonal branch.

Area of distribution

Left atrium

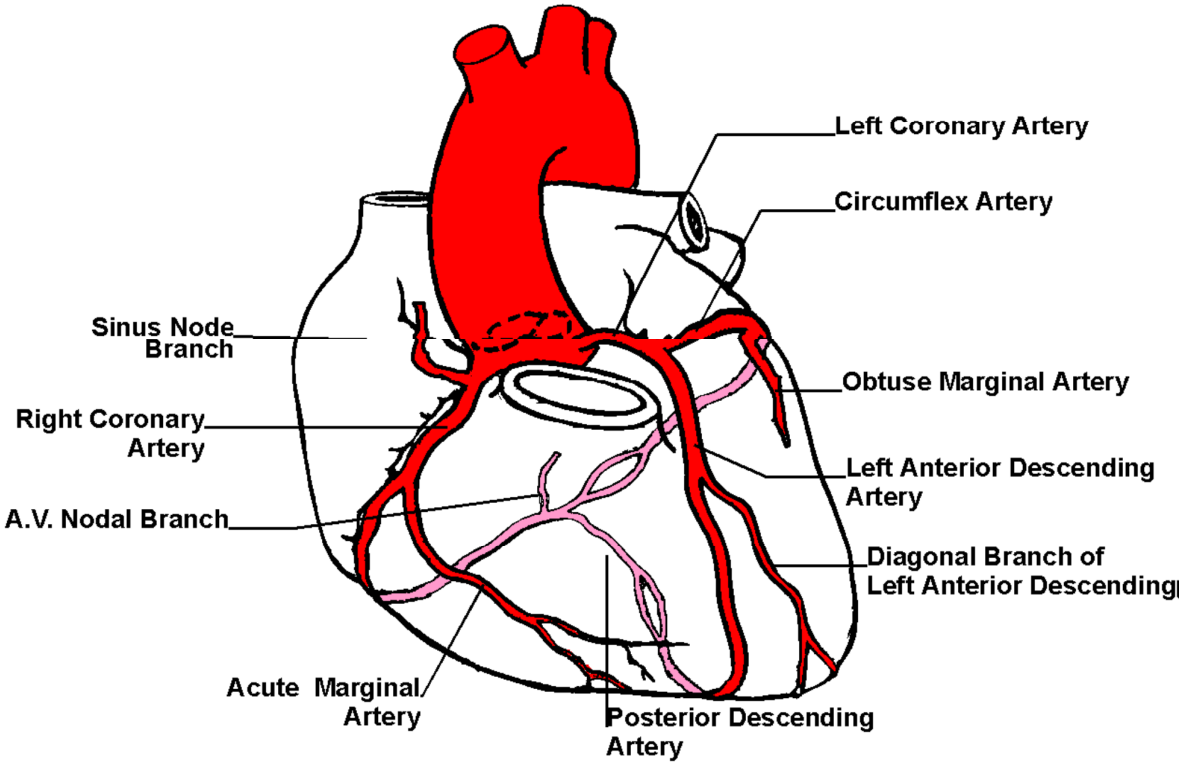
Ventricles

Greater part of the left ventricle except the area adjoining the posterior interventricular groove.

A small part of the right ventricle adjoining the anterior interventricular groove.Anterior part of the interventricular septum.

A part of left branch of AV bundle.

Coronary Arteries



Acute coronary syndrome[96]

They are patients whose clinical presentation cover the following range of diagnosis.

ST segment elevation myocardial infarction

Non ST segment elevation MI

Unstable angina.

The first step is to a detailed description of the symptom complex in order to characterize the chest pain or discomfort. Five descriptors typically are considered in the following.

1. Location,

2. Quality,

3. Duration of the discomfort,

4. Inciting factors, and

5. Factors relieving pain

Clinical classification of angina

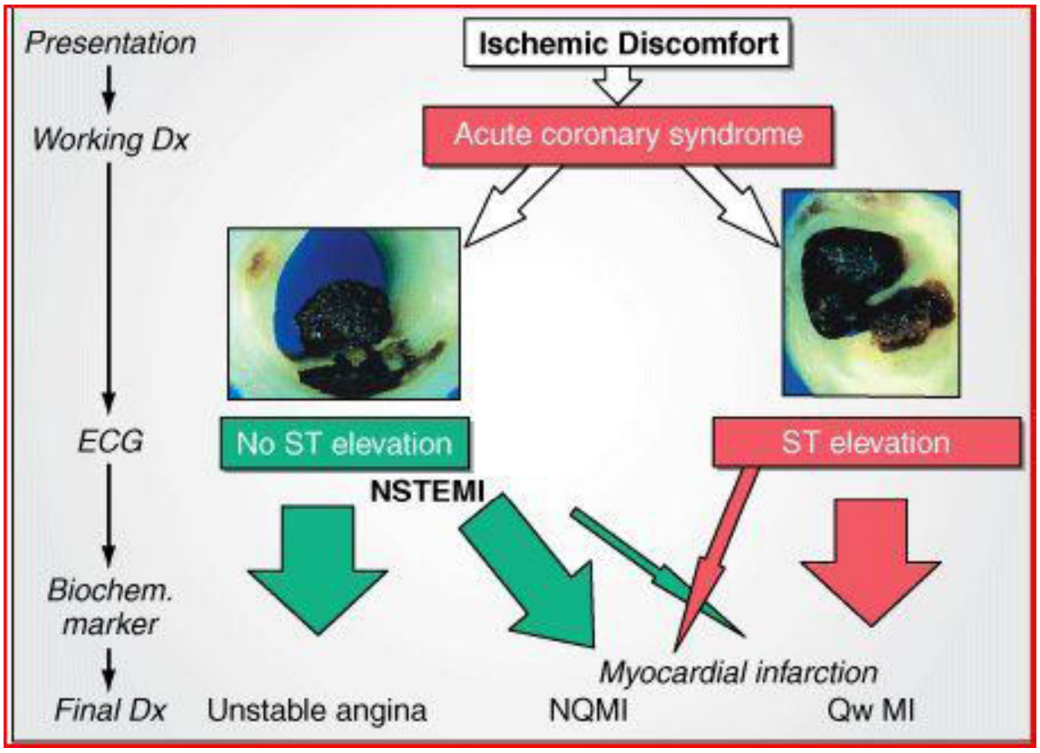
Typical angina (definite)

1. Substernal chest discomfort with a characteristic quality and duration that is

2. Provoked by exertion or emotional stress and

3. Relieved by rest or nitroglycerin.

ACUTE CORONARY SYNDROME



Atypical angina (probable)

Meets two of the above characteristics symptoms.

Noncardiac chest pain

Meets one or none of the typical anginal characteristics.

Stable Angina:

Stable angina is characterized by a deep, poorly localized chest or arm discomfort (rarely described as pain) that is aggravated with physical exertion or emotional stress and relieved within 5 – 15 minutes by rest or sublingual nitroglycerine, or both. The characteristics of the stable angina usually Unchanged for 60 days.

Unstable angina is diagnosed mainly based on clinical presentation[97].

Unstable angina is defined as angina pectoris or equivalent. ischaemic discomfort with atleast one of the three features.

It occurs at rest usually lasting for more than 10 minutes.

Severe and of new onset within the prior 4-6 weeks

Occurs with a crescendo pattern.

Diagnosis of NSTEMI is established if a patient with the clinical features of unstable angina also has have elevated cardiac biomarkers due to myocardial necrosis.

Patho physiology

Plaque rupture or erosion.

Coronary spasm

Progressive mechanical obstruction.

Secondary unstable angina.

Clinical features

Chest pain typically located in the substernal region or sometimes in the epigastrium that radiates to the neck, left shoulder and chin. Anginal equivalents such as dyspnea, fatigue, epigastric discomfort, faintness and eructations..

Crescendo Angina: worsening of angina can be defined as symptoms that result in at least 1 Canadian Cardiovascular Society(CCS) class increase or to at least CCS Class 3 severity.

Secondary Unstable Angina:

This form of unstable angina is precipitated by the imbalance in myocardial oxygen supply and demand caused by condition extrinsic to the coronary arteries in patients with the prior coronary stenosis and chronic stable angina.

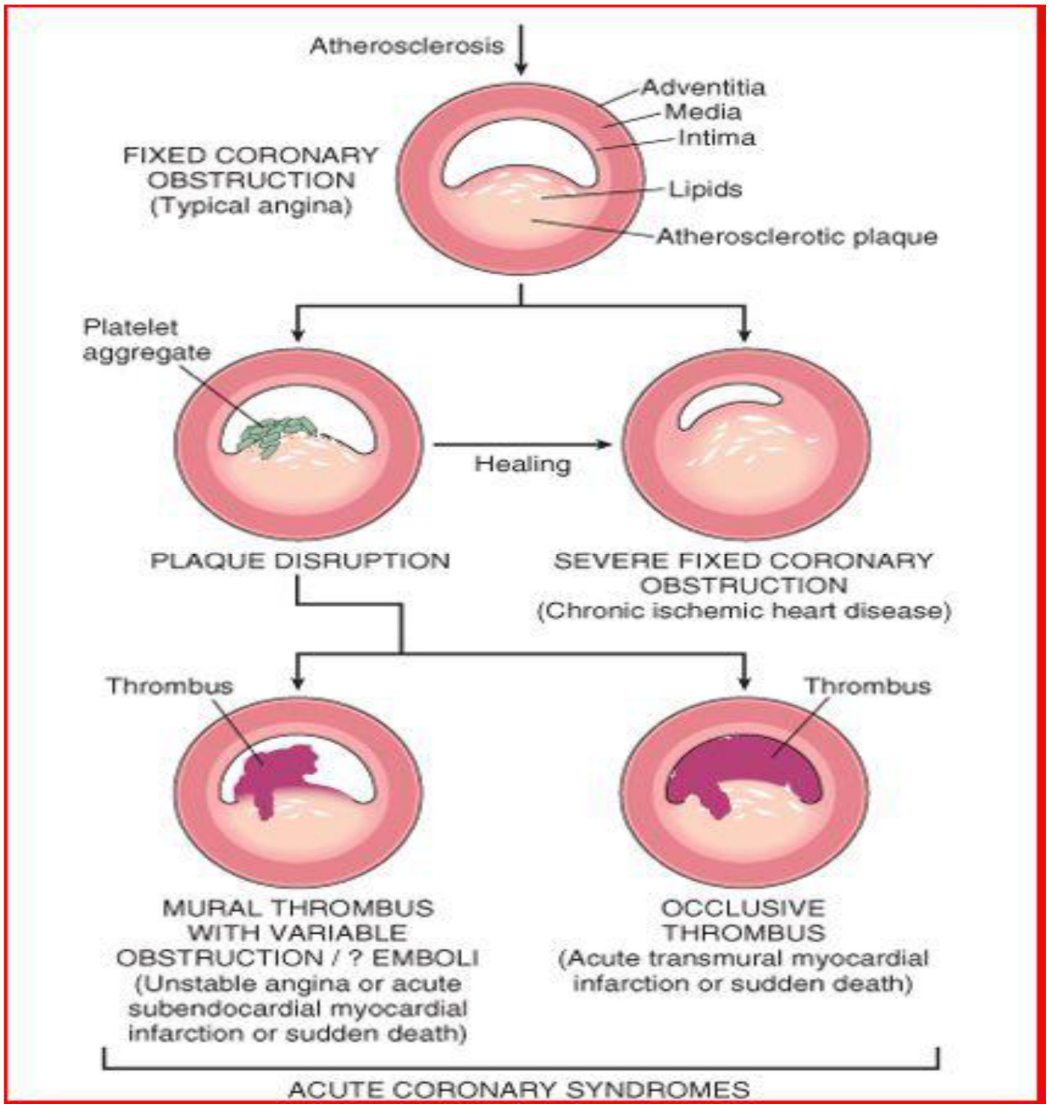
CANADIAN CARDIOVASCULAR SOCIETY(CCS) GRADING:

Grade	Description
Grade I	"Ordinary physical activity does not cause angina." • Walking and climbing stairs. • Angina with strenuous, rapid or prolonged exertion at work or recreation.
Grade II	"Slight limitation of ordinary activity". • Walking or climbing stairs rapidly. • Walking uphill. • Walking or stair climbing after meals. • In cold, or in wind, or under emotional stress. • During the few hours after awakening. • Walking > 2 blocks on the level. • Climbing >1 flight of ordinary stairs at a normal pace and in normal conditions.
Grade III	"Marked limitation of ordinary physical activity". • Walking 1 or 2 blocks on the level and • Climbing 1 flight of stairs in normal conditions and at normal pace.
Grade IV	"Inability to carry on any physical activity without discomfort -- anginal syndrome may be present at rest."

Clinical Circumstances			
Severity	A—Develops in Presence of Extra cardiac Condition That Intensifies Myocardial Ischemia (Secondary UA)	B—Develops in Absence of Extra cardiac Condition (Primary UA)	C—Develops Within 2 wk of AMI (Post infarction UA)
I—New onset of severe angina or accelerated angina; no rest pain	IA	IB	IC
II—Angina at rest within past month but not within preceding 48 h (angina at rest, sub acute)	IIA	IIB	IIC
III—Angina at rest within 48 h (angina at rest, acute)	IIIA	IIIB-$T_{negetive}$ IIIB-$T_{positive}$	IIIC

UA indicates unstable angina; AMI, acute myocardial infarction.

PATHOBIOLOGY OF ACUTE CORONARY SYNDROME



PRECIPITATING FACTORS

Increased Myocardial Oxygen Demand	Decreased Oxygen Supply
• Fever • Thyrotoxicosis • Tachycardia • Malignant Hypertension • Pheochromocytoma • Hypertension • Aortic Stenosis • High Output State • Pregnancy • Drugs: Cocaine, Amphetamine	• Anemia • Hypotension • Hypoxemia (pneumonia, CCF etc.) • Carbon Monoxide Poisoning • Polycythemia Vera • Hyperviscosity Syndromes

The classic World Health Organization criteria for an acute MI[98] require that the **two of the following three elements** be present:

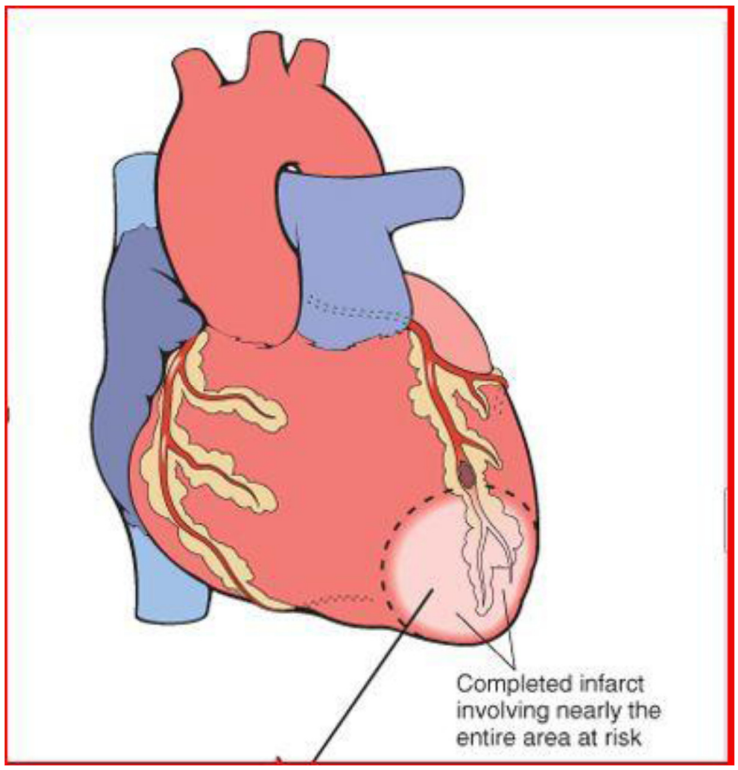
1. A history suggestive of coronary ischemia for prolonged period (>30 min),

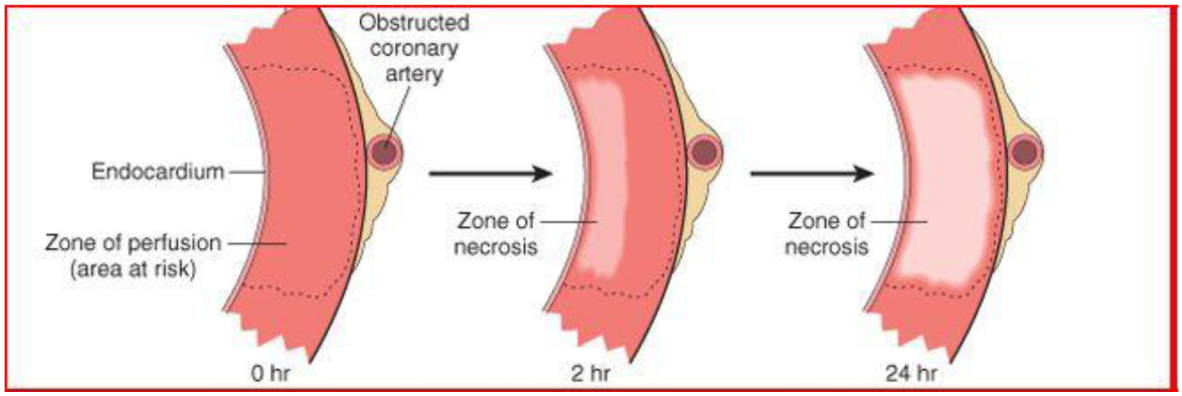
2. Evolutionary changes in the serial ECGs suggestive of MI, ST segment elevation greater than 1mm in two contiguous limb leads and greater than the 2mm in two contiguous chest leads.

3. A rise and fall in serum cardiac markers consistent with the myonecrosis

The pain of myocardial infarction is typically the substernal, diffuse, with a squeezing or pressure quality. It may radiate to the neck or to the jaw, shoulders, or arms. Most often, the pain is accompanied by additional symptoms, such as lightheadedness, nausea or vomiting, diaphoresis, or shortness of breath. The symptoms of the myocardial infarction last longer than 30 minutes, and do not respond completely to the nitroglycerin. Elderly or diabetic patients are prone to atypical symptoms, such as nausea or dyspnea as the sole symptoms of infarction. As many as one fourth of myocardial infarctions are “silent” — that is, whatever the symptoms were present did not impress the patient enough to seek medical care, or even to the remember the incident.

MYOCARDIAL INFARCTION





METHODOLOGY

STUDY DESIGN **:** PROSPECTIVE STUDY

STUDY PERIOD **:** MARCH 2017 TO AUGUST 2017

STUDY POPULATION : About 50 Patients admitted in ICCU

INCLUSION CRITERIA **1.Patients with Acute STEMI, NON STEMI, UNSTABLE ANGINA**

2. Both males and female

EXCLUSION CRITERIA :

1. **Age less than 18 years**
2. **Known coronary artery disease patient**
3. **Patients refusal to participate**
4. **Patients with hypothyroidism**
5. **Patients with familial hypercholesterolemia**

STUDY PLACE **:**Thanjavur Medical College & Hospital, Thanjavur.

INVESTIGATIONS :

- WAIST CIRCUMFERENCE
- BLOOD PRESSURE
- FASTING BLOOD SUGAR
- SERUM TRIGLYCERIDES
- SERUM HDL
- A 12 LEAD ELECTROCARDIOGRAM
- ECHOCARDIOGRAM

STATISTICAL ANALYSIS AND RESULTS

Table 1: Distribution of age in the study groups based on the metabolic syndrome

S. No	Age (in years)	NMS group (n=38)		MS group (n=12)	
		N	%	n	%
1	<40	1	2.6	2	16.7
2	40-49	7	18.4	0	0
3	50-59	15	39.5	5	41.7
4	60-69	12	31.6	4	33.3
5	≥70	3	7.9	1	8.3

Data are expressed as absolute numbers with percentage. NMS = Patients with Acute coronary syndrome only. MS = Patients with Acute coronary syndrome and Metabolic syndrome.

Table2: Comparison of age in years between the groups in the study population

S. No	Age in years	NMS group			MS group			P value	Statistical test
		N	Mean	SD	n	Mean	SD		
1	Overall	38	56.34	9.09	12	55.5	11.8	0.796 (NS)	Unpaired 't' test
2	Male gender	29	54.9	9.55	9	52.7	11.65	0.584 (NS)	Unpaired 't' test
3	Female gender	9	61	5.59	3	63.6	10.02	0.56 (NS)	Unpaired 't' test

Data are expressed as mean with standard deviation. Unpaired 't' test was used to test the level of significance.

Both the group are comparable in respect to age i.e when age factor is considered both the groups are of same age because P value is not significant.

Table 3: Prevalence of metabolic syndrome according to the gender

S. No	Group name	Male (n=38)		Female (n=12)		Overall (n=50)	
		n	%	n	%	n	%
1	NMS Group (Only ACS)	29	76.3	9	75	38	76
2	MS Group (ACS with Metabolic syndrome)	9	23.7	3	25	12	24
P value		0.99 (NS) – Fisher's exact test				--	---

Data are expressed as absolute numbers and percentage.

Fig.1Prevalence of metabolic syndrome according to the gender

Data are expressed as absolute percentage

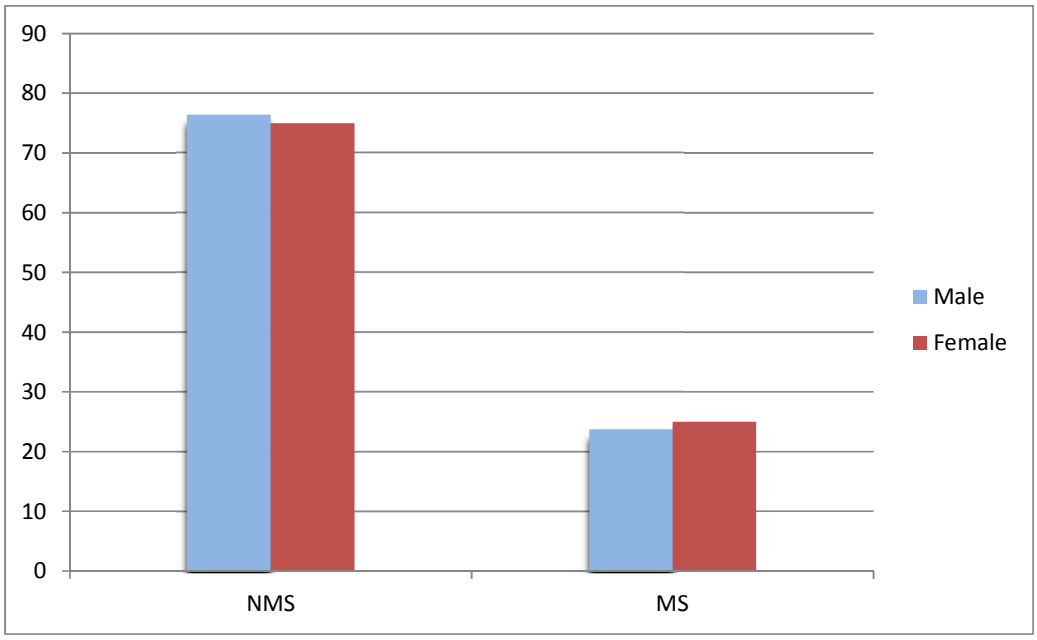


Table 4: Distribution of type of MI of study population between the groups.

S. No	Type of MI	NMS Group (Only ACS) (n=38)		MS Group (ACS with Metabolic syndrome) (n=12)		Overall (n=50)	
		N	%	n	%	n	%
1	ASMI	4	10.5	1	8.3	5	10
2	AWMI	21	55.3	5	41.7	26	52
3	IWMI	10	26.3	4	33.3	14	28
4	NSTEMI	2	5.3	1	8.3	3	6
5	Unstable Angina	1	2.6	1	8.3	2	4

Data are expressed as absolute numbers and percentage.

Table 5: Comparison of the risk factors for the Acute coronary syndrome between the groups.

S. No	Risk factor		NMS Group (Only ACS) (n=38)		MS Group (ACS with Metabolic syndrome) (n=12)		P value
			n	%	n	%	
1	Diabetes	Yes	4	10.5	4	33.3	0.081 (NS)
		No	34	89.5	8	66.7	
2	Hypertension	Yes	6	15.8	8	66.7	0.0016*
		No	32	84.2	4	33.3	
3	Smoking	Yes	7	18.4	1	8.3	0.66 (NS)
		No	31	81.6	11	91.7	
4	Alcohol	Yes	14	36.8	3	25	0.51 (NS)
		No	24	63.2	9	75	
5	Family history of MI	Yes	8	21.1	4	33.3	0.44 (NS)
		No	30	78.9	8	66.7	

Data are expressed as absolute numbers with percentages. Fisher's exact test was used to test the level of significance. Odd's ratio for hypertension is 5.14 (95% CI= 1.8 to 14.4)

Figure 2: Comparison of occurrence of hypertension between the groups in the study population

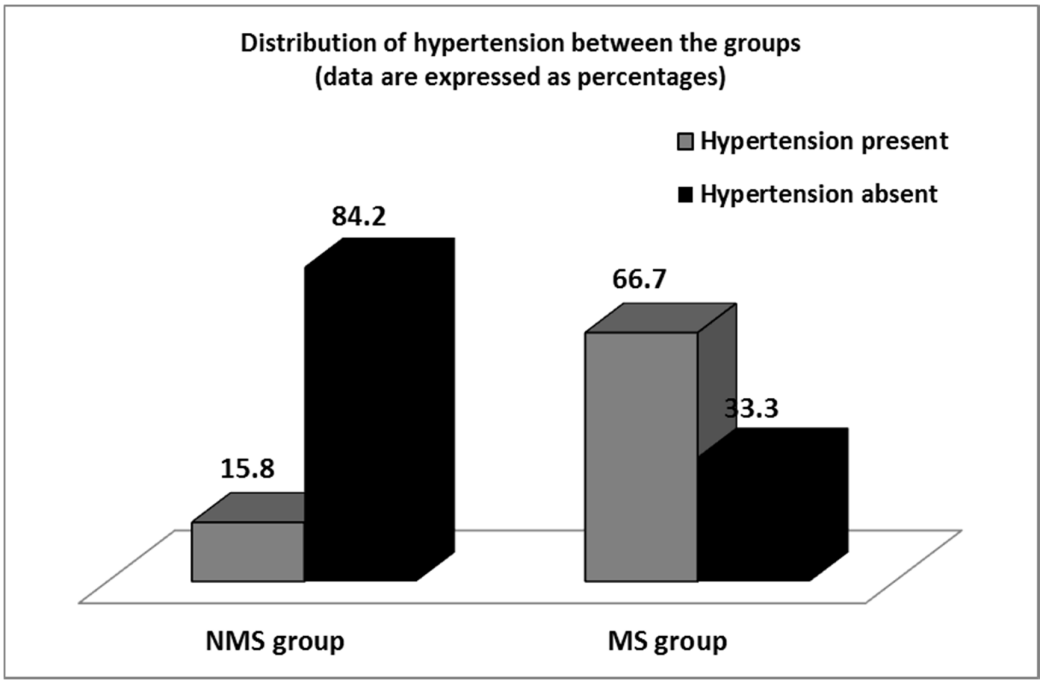


Table 6: Distribution of hypertension grading in two groups of the study population

S. No	Type of MI	NMS Group (Only ACS) (n=38)		MS Group (ACS with Metabolic syndrome) (n=12)		Overall (n=50)	
		n	%	n	%	n	%
1	Normal BP	24	63.2	5	41.7	29	58
2	Stage 1 Hypertension	11	28.9	6	50	17	34
3	Stage 2 Hypertension	2	5.3	1	8.3	3	6
4	Stage 3 Hypertension	1	2.6	0	0	2	4

Data are expressed as absolute numbers and percentage.

Table 7: Comparison of biochemical parameters between the groups in the study population

S. No	Type of MI	NMS Group (Only ACS) (n=38)		MS Group (ACS with Metabolic syndrome) (n=12)		P value	Statistical test
		Mean	SD	Mean	SD		
1	Fasting blood sugar (mg/dl)	91	38.4	143.3	84.2	0.004*	Unpaired 't' test
2	Fasting triglycerides (mg/dl)	88.2	21.5	144	61.7	<0.0001**	Unpaired 't' test
3	HDL (mg/dl)	41	5.73	39.5	6.25	0.44 (NS)	Unpaired 't' test
4	Total Cholesterol (mg/dl)	144.3	29.3	166.2	37.2	0.039*	Unpaired 't' test

Data are expressed as mean with standard deviation. * indicates p value <0.05 which is considered highly significant. ** indicates p<0.0001 which is considered extremely significant.

Table 8: Comparison of waist circumference between the groups in the study population

S. No	Waist Circumference	NMS Group (Only ACS)			MS Group (ACS with Metabolic syndrome)			P value	Statistical test
		n	Mean	SD	n	Mean	SD		
1	Overall	38	81.3	7.2	12	98.3	9.7	<0.0001**	Unpaired 't' test
2	Male gender	29	82.4	7.1	9	98.7	11.26	<0.0001**	Unpaired 't' test
3	Female gender	9	77.5	6.5	3	97	2.64	0.006*	Unpaired 't' test

Data are expressed as mean with standard deviation. * indicates p value <0.05 which is considered highly significant. ** indicates p<0.0001 which is considered extremely significant.

Table 9: Comparison of clinical components of metabolic syndrome between the groups in the study population

S. No	Parameter		NMS Group (Only ACS) (n=38)		MS Group (ACS with Metabolic syndrome) (n=12)		P value	Odds ratio (95% CI)
			n	%	n	%		
1	Elevated waist circumference	Yes	5	13.1	12	100	<0.0001 *	152 (7.8 to 2962)
		No	33	86.8	0	0		
2	High BP	Yes	14	36.8	7	58.3	0.31 (NS)	--
		No	24	63.1	5	41.7		

Fisher's exact test was used to test the difference between the proportions.

Figure 3: Prevalence of clinical components of metabolic syndrome between the groups in the study population. (data are expressed as percentages).

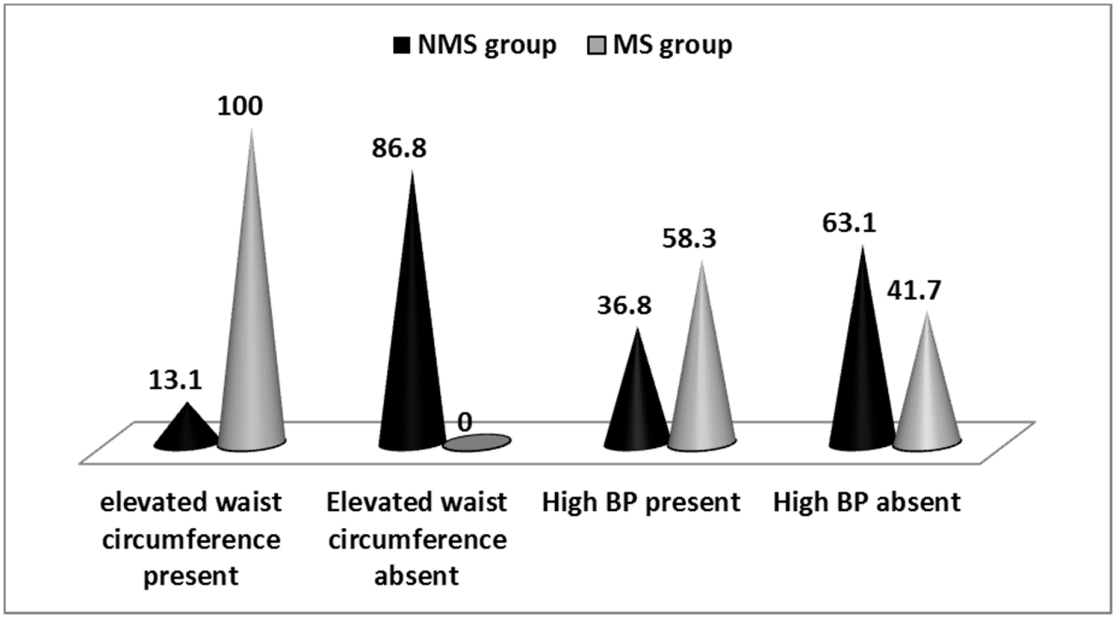
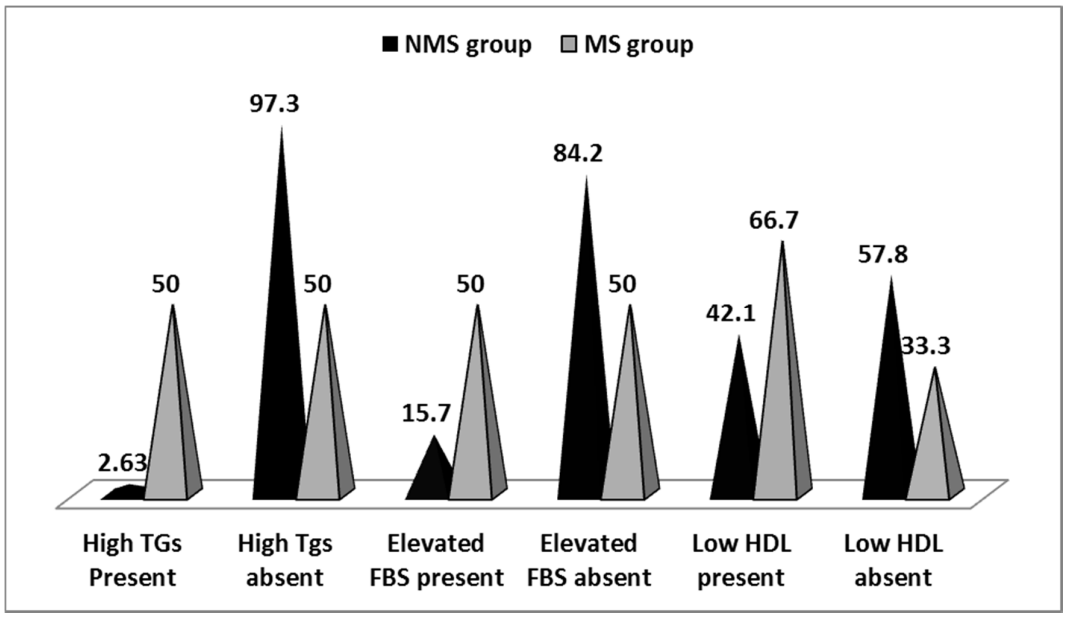


Table 10: Comparison of biochemical components of metabolic syndrome between the groups in the study population

S. No	Parameter		NMS Group (Only ACS) (n=38)		MS Group (ACS with Metabolic syndrome) (n=12)		P value	Odds ratio (95% CI)
			n	%	n	%		
1	High TGs	Yes	1	2.63	6	50	0.0004*	37 (3.7 to 364.1)
		No	37	97.3	6	50		
2	Elevated FBS	Yes	6	15.7	6	50	0.024*	5.33 (1.2 to 22.2)
		No	32	84.2	6	50		
3	Low HDL	Yes	16	42.1	8	66.7	0.19 (NS)	---
		No	22	57.8	4	33.3		

Fisher's exact test was used to test the difference between the proportions.

Figure 4: Prevalence of biochemical components of metabolic syndrome in the groups of the study population



Data are expressed as percentages.

RESULT:

- The prevalence of MS was 76% (76.3% male and 75% female)
- Most of patients found between 41 to 70 years age group.
- Common presentation of ACS was STEMI (80%)followed by the NSTEMI (6%) and unstable angina (UA) (4%) .
- In MS group of patients STEMI presentation was 83.3% followed by NSTEMI (8.3%) and UA (8.3%).
- Fasting glucose was elevated to the extent of 50% in the metabolic syndrome group and it was statistically significant.
- The total cholesterol were increased in both the groups and there was no significance in both the groups.

DISCUSSION.

50 proven cases of acute coronary syndrome who were admitted to the cardiac intensive care unit were selected for analyzing the prevalence of metabolic syndrome. All of them satisfied the inclusion criteria .All patients were subjected to the detailed clinical history and examination. BP was recorded from all patients.12 lead ECG was done whenever indicated. ECHO was done for all patients.

Abdominal circumference of all patients were measured in standing position at a point midway between lower most point of costal margin and upper most point of iliac crest. In a few moribund patients who could not stand, measurement was taken in supine position.

Blood samples were taken for analysis of fasting blood sugar, urea, creatinine and electrolytes on the first day and for fasting blood sugar and lipid profile on the morning of day 3.

In our study the 12 patients who satisfied the criteria for metabolic syndrome were taken as study subjects and the remaining 38 patients who had no metabolic syndrome served as the control group.

Limitations of the study:

- Few sample size.
- NSTEMI was not confirmed by cardiac biomarkers.
- Angiography was not included in the study.
- Other tests like microalbuminuria, which is a part of WHO criteria for diagnosing metabolic syndrome and a good predictor for cardiovascular diseases were not studied.
- Although the risk factors were assessed at the time of index event, the duration of risk factors before MI could not be assessed. Hb A1c was not studied.

CONCLUSION

The prevalence of MS was 76% (76.3% male and 75% female) with IDF-criteria. Number of male patients was higher in the above group. Our study not aimed at a particular population or age group, the bulk of patients found between 41 to 70 years age group.

Out of these 50 patients we found the more common presentation of ACS was STEMI (80%)followed by the NSTEMI (6%) and unstable angina (UA) (4%) . There was no significant difference in prevalence of presenting symptoms. In MS group of patients STEMI presentation was 83.3% followed by NSTEMI (8.3%) and UA (8.3%). In NMS group STEMI was present in 92.1% followed by the NSTEMI (5.3%) and UA (2.6%).

Waist circumference of more than 90 cms in male and > 80 cms in female was prevalent in 100% of the metabolic syndrome group and it showed statistical significance (p=0.0001).

Fasting glucose was elevated to the extent of 50% in the metabolic syndrome group and it was statistically significant (p= 0.024).

Triglycerides was elevated to 50% in the metabolic syndrome group and this also showed to be statistically significant P <0.0004

The total cholesterol were increased in both the groups and there was no significance in both the groups. Though smoking and alcohol was more prevalent in the non-metabolic syndrome group this was not significant statistically.

Among 50 patients studied for the prevalence of metabolic syndrome in patients with acute coronary syndrome the overall prevalence was 76% .

Triglycerides and blood pressure and waist circumference highly influenced the occurrence of metabolic syndrome. Metabolic syndrome is associated with increased risk of devoleping CVD So to prevent the complications due to metabolic syndrome there is a need for early and intensive preventive measures.

BIBLIOGRAPHY

1. Reaven GM. Banting Lecture 1988: role of insulin resistance in human disease. Diabetes. 1988;37:1595-1607.

2.Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults:Findings from the Third National Health and Nutrition Examination Survey. JAMA 2002;287:356

3. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus, provisional report of a WHO consultation. *DiabetMed* 1998;15:539-53.

4. Ineternational Diabetes Federation .Worldwide definition of the metabolic syndrome. Available atwww.idf.org/webdata/docs/IDF_Metabolic_syndrome_definition.pdf.

5.Metabolic syndrome – Harrison's principles of medicine 17th edition vol ii.

6.Zeller M, Steg PG, Ravisy J, Laurent Y, Janin-Manificat L, L'Huillier I, *et al* . Prevalence and impact of metabolic syndrome on hospital outcomes in acute myocardial infarction. Arch IntenMed 2005;165:1192-8.

7. Reaven GM. Banting Lecture 1988: role of insulin resistance in human disease. Diabetes.1988;37:1595-1607.

8. Savage et al., Human Metabolic syndrome resulting from dominant – negative mutations in nuclear receptor –gamma. Diabetes, 52,910-917.

9. Song, Y., Niu, T., Manson, J.E., Kwiatkouski, D., Liu, S.2004.Are variants in CAPN 10 gene related to risk of type 2 diabetes? A quantitative assessment of population & family – based association studies. Am.J.Hum.Genet, 74, 208-222.

10. Weedon, M.N., Gloyn, A.L., Frayling, T.M., Hattersley, A.T.,Datey Smith, G., Ben-shloma, Y.2003a. Quantitative traits associated with the Type 2 diabetes susceptibility allele on Kir 6.2.

11. International journal of paediatric research 2006

12. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. *JAMA.*2002; 287: 356–359.

13. Reaven G. The metabolic syndrome or the insulin resistance syndrome? Different names, different concepts, and different goals. *EndocrinolMetabClin North Am.* 2004; 33: 283–303

14. Sattar N, Gaw A, Scherbakova O, Ford I, O'Reilly D StJHaffner SM,Isles C, Macfarlane PW, Packard CH, Cobbe SM, Shepherd J: Metabolic syndrome with and without C-reactive protein as a predictor of coronary heart disease and diabetes in the West of Scotland Coronary Prevention Study. *Circulation* 108:414–419, 2003

15. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome.*Lancet.*2005; 365: 1415–1428

16. McKeigue PM, Ferrie JE, Pierpoint T, Marmot MG. Association of early onset coronary heart disease in South Asian men with glucose intolerance and hyperinsulinemia. *Circulation.*1993; 87: 152–161.

17. Abate N, Chandalia M, Snell PG, Grundy SM. Adipose tissue metabolites and insulin resistance in nondiabetic Asian Indian men. *J ClinEndocrinolMetab.*2004; 89: 2750–2755

18. Raji A, Seely EW, Arky RA, Simonson DC.Body fat distribution and insulin resistance in healthy Asian Indians and Caucasians.*J ClinEndocrinolMetab.*2001; 86: 5366–5371

19. Nyholm B, Nielsen MF, Kristensen K, Nielsen S, Ostergard T, PedersenSB, Christiansen T, Richelsen B, Jensen MD, Schmitz O. Evidence of increased visceral obesity and reduced physical fitness in healthy insulin resistant first-degree relatives of type 2 diabetic patients. *Eur JEndocrinol.* 2004; 150: 207–214.

20. Apridonidze T, Essah PA, Iuorno MJ, Nestler JE. Prevalence and characteristics of the metabolic syndrome in women with polycystic ovary syndrome.*J ClinEndocrinolMetab.*2004; 90: 1929–1935

21. Hayashi T, Boyko EJ, Leonetti DL, McNeely MJ, Newell-Morris L, KahnSE, Fujimoto WY. Visceral adiposity and the risk of impaired glucose tolerance: a prospective study among Japanese Americans. *Diabetes Care.*2003; 26: 650–655.

22. Hayashi T, Boyko EJ, Leonetti DL, McNeely MJ, Newell-Morris L, KahnSE, Fujimoto WY. Visceral adiposity is an independent predictor of incident hypertension in Japanese Americans. *Ann Intern Med.* 2004; 140:992–1000.

23. Lillioja s, Mott Dm, Howard Bv, Bennett PH, Bogardus C. Impaired glucose tolerance as a disorder of insulin action: longitudinal and crosssectional studies in Pima indians. NEJM 1988; 318:1217-25

24. Aronson D, Rayfield EJ. How hyperglycemia promotes atherosclerosis: molecular mechanisms. Cardiovasc Diabetol.2002;1:1.

25. KoltermanOG,Insel J, Sackow M, Olesky JM. Mechanisms of insulin resistance in human obesity: evidence for receptor and postreceptor defects. J clin Invest 1980;65:1272-84

26. Bonadonna RC, Groop L, Kraemer N, Ferrannini E, DeFronzo RA.Obesity and insulin resistance in humans: a dose response study.Metabolism 1990;39:452-9

27. Abate N, Garg A, Peshock RM, Stray-Gundersen J, Grundy SM.Relationships of generalized and regional adiposity to insulin sensitivity in men. *J Clin Invest.* 1995; 96:88–98.

28. Abate N, Garg A, Peshock RM, Stray-Gundersen J, Adams-Huet B,Grundy SM. Relationship of generalized and regional adiposity to insulin sensitivity in men with NIDDM.*Diabetes.*1996;45:1684–1693.

29. Goodpaster BH, Thaete FL, Simoneau JA, Kelley DE. Subcutaneous abdominal fat and thigh muscle composition predict insulin sensitivity independently of visceral fat. *Diabetes.*1997;46:1579–1585.

32. Kelley DE, Thaete FL, Troost F, Huwe T, Goodpaster BH. Subdivisions of subcutaneous abdominal adipose tissue and insulin resistance.*Am JPhysiolEndocrinolMetab.*2000; 278: E941–E948.

31. Sites CK, Calles-Escandon J, Brochu M, Butterfield M, Ashikaga T,Poehlman ET. Relation of regional fat distribution to insulin sensitivity in postmenopausal women.*FertilSteril.* 2000; 73: 61–65.

32. Nielsen S, Guo Z, Johnson CM, Hensrud DD, Jensen MD. Splanchnic lipolysis in human obesity.*J Clin Invest.* 2004; 113: 1582–1588.

33. Heptulla R, Smitten A, Teague B, Tamborlane WV, Ma YZ, Caprio S2001 Temporal patterns of circulating leptin levels in lean and obese adolescents: relationships to insulin, growth hormone, and free fatty acids rhythmicity. *J ClinEndocrinolMetab*86:90–96

34. Jensen MD, Haymond MW, Rizza RA, Cryer PE, Miles JM. Influence of body fat distribution on free fatty acid metabolism in obesity. *J ClinInvest.* 1989; 83: 1168–1173

35. Petersen KF, Shulman GI. Pathogenesis of skeletal muscle insulin resistance type 2 diabetes mellitus. *Am J Cardiol.*2002; 90: 11G–18G

36. Browning JD, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD,Cohen JC, Grundy SM, Hobbs HH. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. *Hepatology.*2004; 40: 1387–1395.

37. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults(Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment PanelIII) final report.*Circulation.*2002; 106: 3143–342.*JAMA.*2001; 285:2486–2497. NIH Publication No. 01-3670.

38. Grundy SM, Hansen B, Smith Jr SC, Cleeman JI, Kahn RA; American Heart Association; National Heart, Lung, and Blood Institute; American Diabetes Association 2004 Clinical management of metabolic syndrome:report of the American Heart Association/National Heart, Lung, and Blood Institute/American Diabetes Association conference on scientific issues related to management. Circulation 109:551–556

39. Apridonidze T, Essah PA, Iuorno MJ, Nestler JE. Prevalence and characteristics of the metabolic syndrome in women with polycystic ovary syndrome.*J ClinEndocrinolMetab.*2004; 90: 1929–1935

40. Nieves DJ, Cnop M, Retzlaff B, et al. The atherogenic lipoprotein profile associated with obesity and insulin resistance is largely attributable to intra-abdominal fat. *Diabetes.*2003; 52: 172–179.

41. Guerre-Millo M 2002 Adipose tissue hormones.*J Endocrinol Invest*25:855–861

42. Shulman GI 2000 Cellular mechanisms of insulin resistance.*J Clin Invest*106:171–176

43. Ridker PM, Morrow DA 2003 C-reactive protein, inflammation, and coronary risk.*CardiolClin*21:315–325

44. Randle PJ, Garland PB, Hales CN, Newesholme EA 1963 The glucose fatty-acid cycle.Its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus .*Lancet* 1:785–789

45. Ruderman NB, Saha AK, Vavvas D, Witters LA 1999 Malonyl-CoA, fuel sensing, and insulin resistance. *Am J Physiol*276(1 Pt 1):E1–E18

46. Engeli S, Sharma AM 2000 Role of adipose tissue for cardiovascular renal regulation in health and disease. *HormMetab Res* 32:485–499

47. Juhan-Vague I, Morange PE, Alessi MC 2002 The insulin resistance syndrome: implications for thrombosis and cardiovascular disease.*PathophysiolHaemostThromb*32:269–273

48. Okamoto Y, Kihara S, Ouchi N, et al. Adiponectin reduces atherosclerosis in apolipoprotein E-deficient mice. *Circulation.*2002; 106: 2767–2770

49. Hasty AH, Shimano H, Osuga J, et al. Severe hypercholesterolemia ,hypertriglyceridemia, and atherosclerosis in mice lacking both leptin and the low density lipoprotein receptor. *J Biol Chem.* 2001; 276: 37402–37408

50. Wallace AM, McMahon AD, Packard CJ, et al. Plasaleptin and the risk of cardiovascular disease in the West Of Scotland Coronary Prevention Study (WOSCOPS). *Circulation.*2001; 104: 3052–3056.

51. Steppan CM, Lazar MA. Resistin and obesity-associated insulinresistance.*Trends EndocrinolMetab.*2002; 13: 18–23.

52. Grundy SM 2000 Metabolic complications of obesity .*Endocrine* 13:155–165

53. Malmstrom R, Packard CJ, Caslake M, Bedford D, Takinen MR. Effects of insulin and acipimox on VLDL1 and VLDL2 apolipoprotein B production in normal subjects. *Diabetes* 1998;47:779-87

54. Syvanne M, Taskinen Me. Lipids and lipoproteins as coronary risk factors in non-insulin dependent diabetes mellitus. *Lancet* 2997;350 (suppl 1):SI20-33

55. Eisenberg S. High density lipoprotein metabolism. In BetteridgeDj,Illinfworth DR, Lipoproteins in Health and Disease. *London:Arnold*,1999;p71

56. Gardner CD, Fortmann SP, Krauss RM, Association of small low density lipoprotein particles with the incidence of coronary artery disease in men and women. *JAMA* 1996;276:875-81

57. Zambon A, Austin MA, Brown BG, Hokanson JE, Brunzell JD, Effect of hepatic lipase on LDL in normal men and those with coronary artery disease. *ArteriosclerThromb*1993;13:147-53

58. Holvoet P, Kritchevsky SB, Tracy RP, Mertens A, Rubin SM, Butler J,Goodpaster B, Harris TB.*Diabetes.*2004 Apr;53(4):1068-73

59. Krauss RM 1995 Dense low density lipoproteins and coronary artery disease. *Am J Cardiol*75:53B–57B

60. Blake GJ, Otvos JD, Rifai N, Ridker PM 2002 Low-density lipoprotein particle concentration and size as determined by nuclear magnetic resonance spectroscopy as predictors of cardiovascular disease in women.*Circulation* 106:1930–1937

61. Grundy SM 2002 Low-density lipoprotein, non-high-density lipoprotein ,and apolipoprotein B as targets of lipid-lowering therapy. Circulation106:2526–2529

62. Ceolotto G, Valente R. Baritono E, Reato S, Trevisan R. Effect of insulin and angiotensin II on cell calcium in human skin fibroblasts. *Hypertension*2001;37:1486-91

63. Shimamoto K, Hirate A, Fukoka M, Higashiura K, Insulin sensitivity and the effects of insulin on renal sodium handling and pressor systems inessential hypertensive patients. *Hypertension* 1994;23:129-33.

64. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, IzzoJrJL, Jones DW, Materson BJ, Oparil S, Wright Jr JT, Roccella EJ; Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National Heart, Lung, and Blood Institute ;National High Blood Pressure Education Program Coordinating Committee 2003 Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.*Hypertension* 42:1206–1252

65. Kannel WB, Zhang T, Garrison RJ 1990 Is obesity-related hypertension less of a cardiovascular risk? The Framingham Study.*Am Heart J*120:1195–1201

66. Cook DG, Shaper AG, Thelle DS, White head TP. Serum uric acid, serum glucose and diabetes; relationships in a population study. *Postgrad Med J*1986:62;1001-6

67. Quinones GA, Natali A, BaldiS,Frascerra S, Sanna G. Effect of insulin on uric acid in humans. *Am J excretion Physiol*1995;268:E1-5

68. Cook DG, Shaper AG, Thelle DS, White head TP. Serum uric acid, serum glucose and diabetes; relationships in a population study. *Postgrad Med J*1986:62;1001-6

69. Juhan-Vague I, Alessi MC, Vague P. Thrombogenic and fibrrinolytic factors and cardiovascular risk in non-insulin-dependent diabetes mellitus.
Ann Med 1996;28:371-80.

70. Widlansky ME, Gokce N, KeaneyJr JF, Vita JA 2003 The clinical implications of endothelial dysfunction. *J Am CollCardiol*42:1149–1160

71. Heinrich PC, Castell JV, Andus T. interleukin –6 and the acute phase response. *Biochem J* 1990;265;631-36

72. Yudkin JS, Kumari M, Humphries Se, Mohamed-Ali V Inflammation ,obesit;y, stress and coronary heart disease is interleukin –6 the link? *Atherosclerosis* 2000 ;148;209-14

73. .Hu FB, Meigs JB, Li TY, Rifai N, Manson JE. Inflammatory markers and risk of developing type 2 diabetes in women. *Diabetes.*2004; 53: 693–700.

74. Hanley AJ, Festa A, D'Agostino RB Jr, Wagenknecht LE, Savage PJ,Tracy RP, Saad MF, Haffner SM. Metabolic and inflammation variable clusters and prediction of type 2 diabetes: factor analysis using directly measured insulin sensitivity. *Diabetes.*2004; 53: 1773–1781

75. Visser M, Bouter LM, McQuillan GM, Wener MH, Harris TB 1999Elevated C-reactive protein levels in overweight and obese adults.*JAMA*282:2131–2135

76. Ridker PM 2003 Clinical application of C-reactive protein for cardiovascular disease detection and prevention.*Circulation* 107:363–369

77. Catalano C, Muscelli E, Quinones GA, Baldi S, Masconi A, Gibb I ,Effect of insulin on systemic and renal handling of albumin in nondiabetic and NIDDM subjects. *Diabtes*1997;46:868-75

78. Berton G, Citro T, Palmieri R, Petucco S, De Toni R. albumin excretion rate increases during acute myocardial infarction and strongly predicts early mortality. *Circulation* 1997;96:3338-45

79. Berne C, Fagius J, Pollare T, Hjemdahl P.The sympathetic response toeuglycemichyperinsulinaemia.*Diabetologia*1992; 35;873-89

80. Paolisso G, Manzella D, Rizzo MR, Barbieri M , Gambardella A. Effects of insulin on the cardiac autonomic nervous system in insulin-resistant states . *ClinSci*2000;98:129-36.

81. Despres JP, Lamarche B, Mauriege P, et al. Hyperinsulinemia is an dependent risk factor for ischemic heart disease. *NEJM* 1996;334:952

82. AkeTenerz, Anna Norhammar, Angela Silveira, Anders Hamsten, GöranNilsson, Lars Rydén and KlasMalmberg. *Diabetes Care* 26:2770-2776,2003

83. John K. Ninomiya, MSc; Gilbert L'Italien, PhD; Michael H. Criqui, MD,MPH; Joanna L. Whyte, MS, RD, MSPH; Anthony Gamst, PhD; RolandS. Chen, MD. *Circulation.*2004;109:42-46

84. Juhan-vague I ,Alessi MC, Morange PE. Hypofibrionolysis and increased PAI-I are linked to atherothrombosis via insulin resistance and obesity. *Ann Med* 200;32:78-84.

85. Kuusisto J, Mykkanen L, Pyorala K, Laakso M. Hyperinsulinemic microalbuminuria. A new risk indicator of coronary heart disease.*Circulation* 1995;91:831-7.

86. Harrisons principles of internal medicine vol II 17th edition.

87. Harpers textbook of biochemistry.

88. Lipid disorders ACP observer sept 2005.

89. Current and Future Treatment of Metabolic Syndrome and Type2 Diabetes in Children and Adolescents.Diabetes Spectrum October 2005 vol. 18 no. 4 220-228.

90. Diagnosis and Management of the Metabolic Syndrome.*Circulation* .2005; 112:2735-2752.)

91. FusterV.ORowke RA, Walsh RA, Poole – Wilson P.Hurst's TheHeart – Chap 91 – 'Metabolic syndrome, obesity and Diet'.

92. Haffner SM, Alexander CM, Cook TJ et al. Reduced coronary events in simvastatin treated patients with coronary heart disease and diabetes mellitus or impaired fasting glucose levels:subgroup analysis on the Scandinavian Simvastatin Survival Study. Arch Intern Med 1999; 159 (22): 2661-7.

93. Chobanian AV, Bakris GL, Black HR et al. Seventh report of theJoint National Committee on prevention, detection, evaluation,and treatment of high blood pressure. Hypertension 2003; 42(6):1206-52.

94. Gupta A., Gupta, R., Sarna, M., Rastogi Prevalence of diabetes,impaired fasting glucose and IRS in an Urban Indian Population.Diabetes, Res Clin, Pract., 61. (1) 69-75.

95. B.D.chaurashia text book of anatomy volume II.

96. Campeau L: Grading of angina pectoris (letter). Circulation 54:522-523, 1976.

97. Harrisons text book of internal medicine volume II .1527.

98. Pedoe-Tunstall H, Kuulasmaa K, Amouyel P, et al. Myocardial infarction and coronary deaths in the World Health Organization MONICA Project. Circulation 1994; 90:583-612.

A1.PROFORMA

Name	:		Age	:	Sex	: M/F
Occupation	:		IP	:	wd	:

Diagnose :

PAST H/O : T_2DM / SHT / CAD / CKD / PTB / BA / CVA

PERSONAL H/O : SMOKER / ALCOHOLIC /DRUG ABUSE / DIET

FAMILY H/O : CAD / CVA / FAMILIAL TRIGLYCIDIMIA

O/E : PATIENT

CONSIOUS

ORIENTED

TACHYPNOEIC

PALLOR / ICTERVS

CYANOSIS / CLUBBING

PEDAL OEDEMA

CVS : S_1S_2+

RS : B/L VBS +

P/A : SOFT

CNS : NFND

Criteria for Clinical Diagnosis of the Metabolic Syndrome

WAIST CIRCUMFERENCE	
BLOOD PRESSURE	
FBS	
TG	
HDL - C	

ECG :

ECHO :

A2. CONSENT FORM

I _____ hereby give consent to participate in the study conducted by **DR . SANGEETHA.G ,**Post graduate in the Department of General Medicine ,Thanjavur Medical College & Hospital, Thanjavur – 613004 and to use my personal clinical data and result of investigation for the purpose of analysis and to study the nature of disease. I also give consent for further investigations

Place:

Date : **Signature of the participant**

ஒப்புதல் டிவம்

ெ யர் :

வயது :

ாலினம் :

முகவரி:

தஞ்சாவூர் அரசு ருத்துவக்கல்லூரி ருத்துவ னையில் நடைெ றும் இந்த ஆய்வில் முழு சம் தத்துடன் கலந்துகொள்ள சம் திக்கிறேன் .இந்த ஆய்வில் என்னை ற்றி விவரங்களை ாதுகாப்புடன் இந்த ஆய்வில் வெளியிட ஆட்சே ணை இல்லை என்று தெரிவித்துக் கொள்கிறேன் .எந்த நேரத்திலும் ஆய்வில் இருந்து விலகிக்கொள்ளும் உரிை உண்டு என்று அறிவேன் .

இடம் :

தேதி:

கைகெயாப் ம் /ரேகை